Testis

Structure and Coverings:

- They are ovoid in shape 4.5 cm/long 3cm/wide 3 cm Ant. post. diameter
- Volume 15–25 mL. each testis surrounded by 3 Layers:
  - Tunica vaginalis: the outer layer. Consist of 2 layers "parital, Vesiceral" with fluid inbetwean to protect it from trauma. if this fluid become pathologically → hydrocel.
  - Tunica Albugenia: intermedidte. thick, Fibrous, white, Contain Collagen + Smooth muscles that help in Contraction of testicular Capsule to regulate fluid flow.
  - Tunica Vasculosa: inner – highly vascular.

Testicular Vesseles:

[1] Arteries = 3 arteries

ⓐ Testicular artery: (int. spermatic A) a branch from Aorta it's the main blood supply.

ⓑ Vasal artery: branch of inferior vesical artery.

ⓒ Cremastric artery: (ext. spermatic A) branch of inf epigastric artery

NB injury of testicular artery due to (trauma, varicocelectomy, Biopsy) lead to testicular atrophy → infertility

[2] Veins = 3 group of veins

ⓐ Anterior group: (testicular veins) they are 10 veins branchs that anastomose to form pampiniform plexus. they reduce gradually till the ext. inguinal ring to form single testicular vein in which Lt testicular vein drain in Lt Renal vein and Rt testicular vein drain in inferior vena Cava

ⓑ middle groups: (vasal veins) which drain in prostatic plexus, vesical plex.

ⓒ Posterior groups: (cremastric) drain in inferior epigastric vein.

[3] Lymphatics.

Intra testicular Lymph ducts drain finally at para-aortic LN in Lumbar region So that testicular malignancy give metastasis to paraaortic LN region Not inguinal LN region.

Histology of the testis

Tubular Part (seminiferous tubules)

Interstitial Part (the space bet Seminiferous tubules)

[1] Tubular part

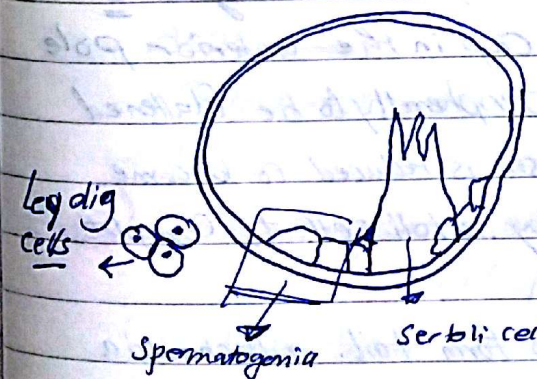
- Each tubule surrounded by 3 Layers:
  - Inner (Collagen) layer
  - middle (Myoid cell)
  - Outer (fibroblast)
- Each tubule consist of basement membrane which Sertoli cell and Germ cell rest on it.
- Germ cells: these cells form the Spermatogenic cells that include different type of cells arranged during maturation from the most primitive cell on basment membrane till the most advanced type of cell near the lumen of seminiferous tubules.

Spermatogonia on basement membrane (4 types) → 1ry spermatocyte → 2ry spermatocyte → Spermatide → Sperm (6 Types)

- Sertoli cell: supporting cells: tall, irregular nuclei, they rest on the basement membrane and send their prolonged cytoplasmic projections towards the lumen.
  they connect with other Sertoli cells by tight junction called "blood testicular barrier."

[2] Interstitial part.

- the space between seminiferous tubules. it contain blood, Lymph vesseles, fibro blastic supporting cells, Macrophages and **Leydig** cell.
- Leydig cells: present in clusters, has round nucleus with prominent mitochondria, endoplasmic Reticulum, Reinke crystals, Lipid droplets.



Function of the testis

Function of Germ cell | Function of sertoli cell | Function of Leydig cell.

NB duration of spermatogenesis starting from spermatogonia till reach the sperm is 74 days and 16 days in epididymis so the total duration is 90 days so Any male treatment should last for 3 months.

I] Function of Germ cell:

ⓐ Proliferation phase:

Spermatogonia 4 types:
- AL (large) → infrequent (rare)
- AD (dark) → inactive
- AP (pale) → active and give the B form
- B → give 1ry spermatocyte

ⓑ Meiotic phase:

1ry spermatocyte (2N) → Replicate DNA → (4N)

(4N) —1st meiotic→ (2N) + (2N) 2ry spermatocyte

(2N) —2nd meiotic→ (N) (N) (N) (N) Spermatid

ⓒ Spermogenesis:

the maturation of spermatid till reach the mature sperm as following:

1. Acrosomal Formation: Golgi apparatus gives the material for Acrosomal formation.
   Acrosome is (modified bag containing lysosomes for ovum penetration) the acrosomal formation passes through 6 stages to to form the acrosomal cap in the anterior pole of the sperm pushing the nucleus peripherally to be flattened with condensed chromatin. the cytoplasm is reduced to become the residual body which phagocytosed by sertoli cell to complete the maturation.
2. tail formation: Migration of centrioles to form tail. mitochondria migrates posteriorly and arranged in spirals around the tail to produce energy.

[2] Function of sertoli cells

Physical and chemical Regulation of spermatogenesis.

(1) physical regulation of spermatogenesis:

- the interaction between sertoli cell and Germ cell help it for propagation from the base to the lumen of seminiferous tubule.
- the mature sperms released from the invaginations of sertoli cell (spermiation) to the lumen
- So the function is Anchoring + transporting + Release of sperms.
- Sertoli cells has actin filaments and microtubules help in morphologic changes in the sperm.

(2) Chemical Regulation of spermatogenesis:

Sertoli cell secretes chemical products that regulate the spermatogenesis:-

(a) Transport and binding products:-
- Androgen bidding protein → transport androgen to the germ cell
- Retinol binding protein → Source of vit A
- Glutaryl transpeptidase → Source of Amino acids.
- SPARC [Secreted Protein Acid Rich in Cysteine] for Ca^+ binding → transport

(b) proteases and Antiproteases:-
- Proteases → proteolysis proteins for energy for germ cell movement, spermiation
- Antiproteases → Protect the sperm from proteases products.

(c) Growth Factors:
- MIS:→ has prenatal, postnatal effect in spermatogenesis.
- Inhibin → regulate FSH secretion (inhibition)
- Activin → " " " (activation)
- Cytokines:- IL_1, IL_2
- Insulin like growth factor (IGF-1) Trans forming growth Factor TGF α,β

(d) Immunological protection of spermatogenesis through TGF β that protect the sperm in the testis, vagina Cause it activated in acidic pH of vagina.

NB MIs is Mullerian Inhibitory Substance.

[3] Function of Leydig cell.

Androgen biosynesthesis

- Formation of Androgens by Leydig cell under the effect of pituitry (LH)
- 1st step is Formation of cholesterol either By LDL or Denovo in Leydig cell from Acetyl Co enzyme A.

- Cholesterol $\xrightarrow[(P450)]{\text{enz cytochrome}}$ Pregnenolone $\longrightarrow$ testosterone (end result)
- testosterone transported in blood stream in 3 Forms :
  - bound to Albumin 54%
  - Sex hormone binding globulin (SHBG) 44%
  - Free testosterone 2%.
- testosterone is trans formed into 3 Forms :
  - testosterone : the main form. it acts on muscles, testis, some nervous areas.
  - DHT : acts on epididymis, vas deferanse, Prostate, Seminal vesicle.
  - Estradiole (E2) : Formed by aromatization of testosterone it's the active Form of testosterone in Nervous tissue.
- Effect of androgens :
  1. Prenatal : development of Ext, int genital duct + testicular descent.
  2. Post natal :

CNS → sexual desire, elevated mood, self confidence.
CNS → -ve feed back mechanism to inhibit release of (GnRH, LH) after aromatization to Estrogen.

Reproductive system → testis : Spermatogenesis
Reproductive system → Int genitalia : development of epididymis, Vas, Seminal vesicle. NB → ↓ androgen → Atrophy + Aspermia
Reproductive system → Ext. genitalia : testosterone and DHT are responsible for penile growth before puberty Not After

Metabolic System → Muscle → ↑ muscle mass by hypertrophy of Fibers Not ↑ in Numbers.
Metabolic System → Larynx → growth → deep voice
Metabolic System → bone → testost. + Estrogen → ↑ bone density + epiphyseal closure.
Metabolic System → Skin → ↑ secretion of seb gland → Acne, hair growth
Metabolic System → Blood → Synethesis of RBC, Hb

Epididymis

- Narrow tightly coild tube, Comma-shaped, Connected the efferent ducts From the testis to vas deferens.
- it's Lie at the superior, postero-lateral surface of the testis
- Divided into:
  - head (Caput)
  - Body (Corpus)
  - tail (Cauda)
- Histology:
  - Columnar cells (the main cells: tall, ciliated, PAS +ve)
  - Basal cells (Pyramid shape, Contractile, Actin +ve)
  - clear cells mainly at the tail region.
- Function of epididymis:
  1. Sperm transport by: ① hydrostatic pressure from fluid secretion in testis.
     ② Motile cilia.
     ③ Rhythmic Contraction of Contractile muscles.
  2. Sperm maturation by:
     ① Attain sperm motility by secreting L-Carnitine & α-glucosidase.
     ② Attain sperm fertilization ability by:
     ① ↑ glycolysis, ↑ -ve charge on the sperm surface
     ② ↓ Sperm creatin Kinase
     ③ Secretion of Glycerophosphoryl choline, inositol, zinc which are essintial for sperm maturation.
     ④ Secretion of Sialic acid essential for integrity of the acrosomal membrane.
     ⑤ D-glucosidase: facilitate sperm-ovum binding.
  3. Sperm protection:
     (a) From chemical damage through secretion of proteinase inhibitors and anti oxidants.
     (b) From Immunological damage through blood epididymal barrier, Production of Factors inhibite T cell activation.

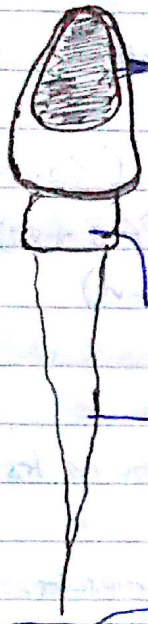
Epididymal markers:

1. L-Carnitine
2. 5α glucosidase
3. Glycerophosphoryl choline

Physiology of the sperm:

1 Structure of the sperm:

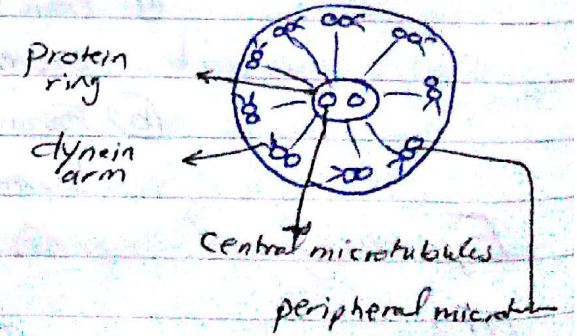
it's 60 um length, Flagellated, has No cytoplasm.



- **Head** → oval in shape, Contain nucleus → Surrounded anteriorly by
  - **Acrosome** → membrane-bound organelle
    - Contain the enzymes essential for penetration of the layers surround the oocyte before fertilization
    - occupies 70% of the sperm head in the front of nucleus.
- **Neck** → posterior extension of the Head.
  Connect Head to tail termed (Connecting peice)
- **Tail** → the central core of the entire tail called **Axoneme**
  according to the surrounding layers of the axoneme the tail is divided into 3 parts:

Mid-peice	Main-peice	End-peice.
* area Follows the neck	* termed principle peice	* the distal end of tail
* Axoneme surrounded by Spirally arranged Mitochandria. it's the energy source of sperm.	* devoid of mitochondria * surrounded by Fibrous sheath.	* Not surrounded by Mitochondria or Fibrous sheath
* 5 um in length.	* 45-50 um length.	* 5 um length.

The Axoneme: is composed of 2 central single microtubles surrounded by a protein ring which joins up to (9) doublet microtubules peripherally by radial spoks (Links) like a wheel. each of these (9) microtubules Contain 2 arms (dynein arms). the (9) microtubules Called A and B



Funchon of the Sperm:

1. inside male genital tract.
2. inside femal genital tracts
   - a. inside cervix, uterus.
   - b. inside fallopian tube.
   - c. Sperm ovum interaction.

[1] Function of the sperm inside male genital tract:-

(a) Sperm motility:-

- the non motile testicular sperms → transformed to motile sperms in the epididymis.
- the energy required for sperm motility obtained from mitochondria

$$ATP \xrightarrow[\text{dephosphorylated}]{ATPase} ADP + \text{energy}.$$

Mechanism of Sperm motility:

(a) the ATPase enzyme is activated in one half of the axoneme that forms the central core of the sperm tail → Accordingly → the dynein arms will pull on the adjacent doubles of microtubules of this side leading to their sliding → with subsequent binding of the tail in a specific direction.

(b) then the process of activation and sliding is switched to the opposite half of the axoneme leading to binding of the tail to the opposite direction.

(c) the sperm motility is obtained as a result of co-ordination between alternative movements and bends of the sperm tail.

(b) Sperm fertilizing ability:

- testicular sperms has no fertilizing ability. they obtain their fertilizing ability inside the epididymis.

[2] Function of sperm in Female genital tract ← Cervix - uterus, Fallopian tubes, Sperm-ovum interaction

(A) Sperm function inside cervix, uterus:

- the main function is penetration of cervical mucus, migration through the uterus.
- 3 stages of sperm transport:-

(1) **Rapid transport:** 10-20 minutes.

- occurs immediately after deposition of the semen into the vagina
- Sperms are transported into the cervical canal via the uterine contration during coitus.

(2) **Colonization of sperm Reservoirs:** takes up to 48 h after coitus.

- Massive numbers of sperms are colonized inside cervical folds, crypts to form Reservoirs
- This phase depends on the presence of ovulatory cervical mucus which:
  - (a) direct the sperm towards the Folds, crypts
  - (b) ↓↓ Leucocytes → ↓↓ phagocytosis of the sperms.

③ Slow Release and transports

- After adequate sperm reservoirs are established → sperms are released sequentially for prolonged periods
- the slow release is helped by:
  - Sperm motility.
  - Contractile activity of myometrium → Help transport of sperms to fallopian tubes

(B) Sperm function inside fallopian tubes:

① Sperm Capacitation

- Normally the ejaculated sperms are not capable of fertilization as the seminal plasma contains decapacitation factors that prevent premature fertilization before the sperm reaches the oocyte.
- Sperm capacitation means that these decapacitation factors are separated from the sperms during their transport through the cervix, uterus, F. tubes.
  - when they become separated from seminal plasma (3–4 hours) during this capacitation the sperm membrane show some changes:
    - (a) Destabilization and increased permeability.
    - (b) Efflux of cholesterol
    - (c) Influx of Ca, Na, K, glucose, oxygen.

② Sperm hyperactivation

- means increase of amplitude of the bending of the sperm tail → with subsequent decrease in the progressive sperm motility.
- they main attain circular type of motility
- this hyperactivation of motility helps (in) the penetration of the sperms through the layers that surround the ovum.

C) Sperm-ovum interaction:

- the sperm reached the site of fertilization [Ampulla of Fallopian tube]. passes through the coverings of the ovum:
  - ▸ Cumulus oophorus ▸ Corona radiata ▸ Zona pellucida.
- then enter into the periuterine space → Finally penetrate the vitelline membrane of the ovum into it's cytoplasm to Completete the process of fertilization as Follows:

1. Penetration of Cumulus oophorus:
   depend on → physical factors (sperm hyperactivation)
   → Chemical Factors (hyaluronidase enzyme that digest the hyaluronic acid matrix of the cumulus layer)
2. Penetration of Corona radiata:
   depend on Corona-penetrating enzyme (estrase enzyme)
3. Zona binding:
   depends on the interaction between specific receptors on the sperm surface and specific proteins (ZP3) of the Zona pellucida.
4. Penetration of Zona pellucida (Acrosomal Reaction)
   The acrosom Contain proteinase enzyme in an inactive form [Proacrosin] which Found in the inner acrosomal membrane.
   acrosomal reaction means activation of this Pro acrosin enzyme to active Form (acrosin) and it's release by Formation of multiple fusion points between sperm plasma membrane and the outer acrosomal membrane. then openings are formed at these points → Finally. the fused membranes are dispersed as multiple vesicles and acrosin released From inner acrosomal membrane to Help the sperm binding and penetration of Zona pellucida.
5. Zona reaction: after the sperm penetration this reaction occurs to hardening the Zona to prevent further penetration of any other sperm. this is mediated by Neuraminidase like enzyme From the sperm.
6. Fertilization: after the sperm passes the Zona pellucida it enter into the perivitelline space → fuse with vitelline membrane of the ovum ⟹

Continue Fertilization process:-

at the same time there is :

① chromosomal material condense inside the ovum to Form [Female pronucleus]

② Sperm enters into the Oocyte cytoplasm to Form [Male pronucleus].

the male pronucleus migrates into the female pronucleus and Now this is a Fertilized oocyte that is called Zygote.

Clinical Evaluation of Infertility in males

History

- ▷ infertility history [4P]
- ▷ Sexual history [4I]
- ▷ Medical history ABCD
- ▷ Surgical history 4 areas

Examination

- ▷ General examination
- ▷ Genital examination

① History

Infertility History:

- ◉ **P**erid of infertility: investigations of infertility should start after one year of unprotected marital relations.
- ◉ **P**revious pregnancy:
  - 1ry infertility: the male never impregnated a female before.
  - 2ry infertility: " " has " " "
- ◉ **P**revious Treatment:
  - Androgenic steroids medications Lead to suppression of gonadotropins and spermatogenesis
- ◉ **P**artener evaluation: is very important and prognostic.

Sexual history: 4 I

- **Impotance:** (Erectile dysfunction)
  Lead to infertility due to Failure of deposition of the sperm inside the vagina
- **Intromission problem:**
  due to: ↓ vaginal lubrication. ▲ using saliva
  ▲ using surgical lubricant (KY geL)
  that affect sperm motility.
  NB. Peanut oil and safflower oil are more safe.
- **Intravaginal ejaculation:** ejaculation should be intravaginally to produce pregnancy
  Causes of Extra vaginal ejaculation:
  - ▲ Sever premature ejaculation
  - ▲ Sever hypospadias.
  - ▲ Retrograde ejaculation
  - ▲ An ejaculation.
- **Inter Course timing + Frequency:**
  - high frequencey is very rare of infertility
  - Low frequnacy " " " " " Cause it may be not in the ovulation days of wife.
  - Ideal frequency is every 2 days.

NB Doctors Recommendations of inter course in a Certain time and Certain day may Lead to stress of the Couples → Sexual failure.

Medical history: ABCD

Age: old men → ↓ Leydig cell but still in fertile function
old women → ↑ FSH, ↓ ovarian Function

Behavior, occupation:

- Addiction and Abuse agents: Opiates, alcohole, Cannabies, Cocaine distrubute male repoductive system.
- Anarobic steroids → ↓ Gonadotropins, ↓ Spermatogenesis.
- Foods: Animals which eats oestrogenic compounds → infertility.
- heat
- Herbicides, insecticides
- heavy metals: Lead, Arsenic, Hg

Cigarette smoking: ↑ abnormal Forms and ↓ sperm Count

Disease Fever → ↓ spermatogenesis
Some diseases → Erectile dysfunction.

Surgical history:

- Abdominal area operations: LN dissection may lead to sympathetic Nerve enjury → ejaculatory Failure.
- Pelvic area operations:
  - Prostatectomy → bladder neck operation. may affect ejaculation
  - Inguinal hernia repair: may lead to injury of vas deference espicially if done during childhood
- Penile area operations: urethral stricture repair, hypospadias, epispadius.
- Scrotal area operations:
  - Congenital → testicular mal descent
  - traumatic → trauma, torsion
  - operative → Scrotal hydrocelectomy, Testicular biopsy varicocelectomy.

② Examination

General Examination

- manifestation of Hormonal disorders
- " " systemic "

Genital Examination

- penis – testis – Epididymis
- vas deferens – spermatic cord

General Examination

ⓐ manifestations of hormonal disorders: (Skeletal manifestations, Breast manifestations)

- Skeletal manifestations:
  - Body Fat: over weight may associated with ↓ testicular volume, ↓LH, ↓testosterone.
    ↑ Aromatization of testosterone → ↑ Oestrogen → Abnormal spermatogenesis
  - Disturbed body propotions.
- Breast manifestations: gynecomastia may associated with ↓ Androgens, ↑ prolactin, ↑ oestrogen as in Klinfelter Syndrome
- Skin manifestations: ⊙ Androgen defeciency lead to loss of terminal hair and straight Frontal hair line and Transverse upper border of pubic hair. ⊙ Anaemia → Pale skin ⊙ dry skin due to ↓ action of seb. glands.

⑥ manifestations of systemic disorders:-

: the pt is examined For visual Field defect and (Anosmia) smell loss chest, Renal, Hypertension.

: Kallaman syndrome: genetic disorder characterized by Faiture of start puberty or Failure to Compelete it. in addition to symptoms of hypogonadism, inability to smell ← Absent Loss (Anosmia) / higlly reduced (Hyposmia)

Genital Examination.

Penis: Examination of length, urethral opening, Erectile dysfunction.

Testis: ⊙ Standing position → testis should be in scrotum

⊙ Abnormal places: Scrotal neck, inguinal canal, ectopic, Absent, impalpable

⊙ Axis: vertical Abnormal horizontal testis due to recurrent attacks of testicular torsion. Fixed by [Orchiopexy]

⊙ Size: in supine position to avoid syncope measured by 2 methods:

① orchidometer → volume Normally (16–20) mL.

② Special Calipers measuring Length, width. Volume = $W^2 \times L \times \pi/6$

Normal length 3-5 cm. width 2.5 cm.

⊙ Consistency: by gentil pressure it's rubbery Abnormal findings:

① soft → impared spermatogenesis ② small, hard → KlinFelter.

③ large, Hard → tumour.

⊙ Physiological megalotestis or Macro-orchidism means symmetrical increase in testicular volume, according to Races, Stature. also it occurs in excitation, Plateau stages of sexual response cycle.

Hydrocele should be excluded by Transillumination or By U/S

⊙ Cancer testis → infertility (30:1)

Epididymis: soft. Felt in upper pole and posterior surface and lower pole of testis.

Vas deferens: thin, Firm tube among the Soft spermatic Cord.

Spermatic cord: Examined For the presence or abscence of Varicocele.

Prostate: Examined for infection, Consistency

Hard nodules in prostate means (Calcification or Cancer)

2 measures Should be taken ① PSA = prostatic specific antigen and TRU (Trans rectal ultrasound)

② Androgen therapy should be Contraindicated to avoid Flairing of Carcinoma.

Semen Analysis

Instructions:

[1] Abstinence 2-7 days [2] clear sterile container [20-40°C]
[3] Sample should Not be stay out lab. For more than 1 hour.
[4] Better to do 2 analysis with 1-3 weeks interval.
[5] Condome is contraindicated cause it contain spemicidal materials.
[6] if culture will be done the pt' should pass urine Frist.
[7] Cotius interruptus: is Not good because loss of the 1st portion of ejaculation which is very rich in sperms.

Physical Examination: Colour, Odour, Volume, Vescosity, Liquifaction, PH

① Colour:

Normal: greyish white cause it's high protein content.

Abnormal: → yellow due to: bilirubin → in hepatic → Carotinemia
: urine → bladder neck dysfunction
: Yellow + soliod clumps → infection.

→ Red_brown due to:
• drugs → Rifampacin.
: blood (Haemospermia) → Pink Fresh leftel blood
→ bright red Fresh excess blood
→ brown → old excess blood
due to:
① genital infection (TB, ₿) ② tumour ③ blood anomalies

② Odour:

it's affected by drugs or food.
• urineferous → urine contamination (Retrograde ejacut, bladder neck dysfunction)
• offensive → genital infection

③ Volume:

Semen is measured by graduated cylinder.
Normal volume 1.5mL (2010) 2-5mL (1999)
Abnormal findings (Aspermia - oligosperma - Hyperspermia)

⊙ Aspermia: Complete absence of seminal fluid.

⊙ Oligospermia = Hypospermia = parvespermia means volume < 1.5 mL due to:
- bad collection of the sample
- Retrograde ejaculation
- short period of Absitence.
- Absence of vas or seminal vesicle.
- Ejaculatory duct obstruction (Partially)
- Hypogonadism.

⊙ Hyperspermia: volume > 6 mL
may cause infertility due to:
Hyperspermia lead to Relative oligozoospermia
" " Loss of large amount of semen/sperm

N.B spermia: related to seminal fluid and Zoospermia → Related to sperms.

(4) Liquifaction:-

⊙ Semen should be Liquified (to be in the liquid form) within or after 30 minutes (in vitro) and 5 minutes (in vivo)

⊙ Normally the semen is released in a Coagulated or gel form because of the effect of Co-agulating enzyme of seminal vesicle (Protein Kinase). then it's Liquefied by the Liquefiying enzymes of the prostate (Fibrinolysin, Fibrinogenase, Aminopeptidase).

⊙ Abnomal findings:
(1) Non Coagulated semen → No coagulating enzyme → CBAV
Congenital bilateral absent of Vas or Ejaculatory dysfunction
(2) Non Liquefied semen → No Liquefiying enzymes → poor prostatic secretion
it appears as gelatinous clots inside the liquid
Rx: α chymotrypsin OR Lysozyme OR Bromelain (1gm/L)

(5) Viscosity:

it is the ability of the Liquefied semen to poured drop by drop from wide pore pipette

Normally: Liquefied semen is poured drop by drop.

abnormally: ↑ viscosity makes the semen droped as a threads more than 2 cm
this can cause infertility due to: Failure to coat the cervix and drain outside the vagina, and impaire sperm movement.

⑥ PH: Normally 7.2 – 8 ie alkaline
it's controlled by ① acidic secretions of the prostate.
② Alkaline secretions of the seminal vesicle.

Abnormal findings:
① PH < 7.2 + Normal volume → infection (Pyospermia)
② PH < 7.2 + ↓ volume due to → Congenital bilateral absence of vas
Retrograde ejaculation
Ejaculatory duct obstruction.
③ PH > 8 → chronic infection of prostate.

Microscopic Examination of the sperms:

① Sperm Concentration ② sperm motility, viability ③ sperm morphology.
④ Sperm agglutination ⑤ Sperm antibodies ⑥ Non sperm cells.

i) Sperm Concentration:

- Counting methods: 1 Neubauer haemocytometer → Needs dilution.
2 MaKler Counting chamber → No need for dilution
3 Microcel chamber → No need for dilution.
- Normal → 2010 sperm count/mL → 15 million/mL or more
or total sperm count/ejaculate → 39 million/ejaculate or more
1999 sperm count/mL → 20 million/mL or more
total sperm count/ejaculate → 40 million/ejaculate or more.
- Abnormal Findings:
ⓐ oligozoospermia < 15 million/mL Causes: ① loss of 1st portion of semen
② short period of Absitence.
③ E. D obstruction
④ high volume → Relative dilutional oligozospermia
ⓑ polyzoospermia > 250 million/mL
Causing infertility due to ① ↓ sperm motility
② ↓ sperm fructose
③ Spontaneous abortion in wives.

(c) Azoospermia: Compelete absence of the sperms in the ejaculate.

(d) Cryptozoospermia: means that some semen shows azoospermia (but) after centrifuge it shows the hidden sperms.

▸ DNA flow cytometery:

it's a good method for detection of sperm concentration. it's based on that the Haploid sperm cell is differ in DNA staining with other diploid cells in the ejaculate. so it's Rapid, confirmed method.

[2] Sperm motility, viability:

5 microscopic fields are assessed to classify 200 sperms { quantitative / qualitative

⊙ quantitative: by counting numbers of motile, Non motile to know percent of motile sperms.

⊙ qualitative: to measure quality of sperm motility.

Grade A: → Rapid progressive more than 25 μm [5 heads or ½ tail]
Grade B: → slow progressive 5–25 μm
Grade C: → Non progressive Less than 5 μm.
Grade D: → Non motile.

⊙ Normal findings:

	2010	1999
A+B	> 32%	> 50%
A+B+C	> 40%	A > 25%
viability	> 58%	> 75%

⊙ Abnormal findings:

▸ Asthenozoospermia: means A+B < 32% oR A+B+C < 40%

▷ Non motile sperms may be actual immotile (live) or dead called Necrozoospermia.

▷ there are 2 methods to differentiate between Live or dead sperms: ① Dye exclusion method
② HOST [Hypo-osmotic swelling test]

[A] Dye Exclusion method:

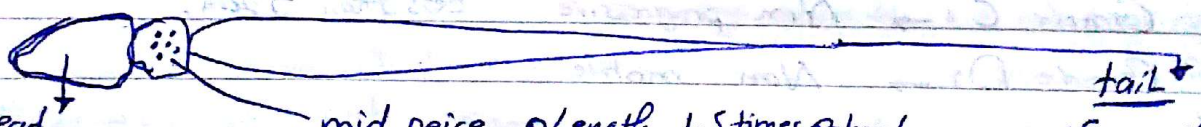
- depend on dead cells with damaged cell membrane take up specific stains while Live cells are Not take stain.
- test: 1% eosin y added to semen then 10% Nigrosin to provid dark background to improve vision.
- Result: : dead sperms appears Red : Live sperms appears white

[B] Hypo-osmotic swelling test. (HOST):

- based on Live cell with intact cell membrane make them swell at the tail under hypo osmotic condition. while dead cell Not swell Cause of damaged cell membrane.

[3] Sperm morphology:

- Semen should be stained first by [Papanicolaw or Bryan Leishman stain or Giemsa stain]
- Sperm should have the following criteria:



head
Round (oval-smooth)
Length (3-5 micron)
width (2.5-3.5 micron)
Acrosome 40-70% of the head surface

mid peice
- Length 1-5 times of head
- width 1 micron
- Contain cytoplasmic droplets

tail
uniform, thinner than mid peice, Free From Kinks, Un Coiled

- these criteria are called Kruger's Strict criteria of morphology (SCM) it has a relation with IVF as:

Men with SCM > 14% have Fertilization rate 91%
" " " < 14% " " " 37%

- Abnmal forms: 2010 = < 96% 1999 = < 80%

Abnormal findings:

① Teratozoospermia: abnormal Forms > 96%

Causes: * UnKnown (most cases)
* Infection
* Defective spermatogenesis
* Coeliac disease
* chron's disease
* Hodgkin's diseas

⊙ Teratozoospermia index (TZI) = Number of defects / Number of abnormal sperms
[(Multiple anomelies index (MAI)]

Normally TZI range from 1-3
if it's equals ① it means one defect in one sperm.
if it equals ③ it means 3 defect in one sperm.
if the index > 1.5 → Reduced fertility.

② Oligo atheno teratozoospermia (OAT) syndrome = Stress pattern

it means defect of the three sperm parameters ← count, motility, Morphology.
it's found in * varicocel * heat exposure * Fever * irradiation

③ Globozoospermia: Round-head

structural abnormality in the spermatogenesis in which golgi apparatus is not transformed to acrosome needed for fertilization. So that the sperm can not interact with the egg (failure in penetration)

(NB) Abnormalities of the head → Larg oval ⬭, Small rounded ○, Tapering ◇, pyriform ⬯

Abnormalities of the tail → Double tail, Coiled, Absent

Motile oval index (MOI): evaluation of the three sperm parameters in the same time.

MOI = Count x Motility x oval sperm.

minimum standerd 20 x 4 x 60 = 4-8 million/mL

4 Sperm Agglutination.

- it means stuck of sperms to each other by antibodies.
- usually they are motile and rarely attach to other cells or debris.
- they stuck head to head OR midpiece to midpeice OR tail to tail
- if this agglutination is seen → Immunological tests should be done

NB Sperm Aggregation: means the dead sperms stuck with other cells or debris. it occurs in small clumps in normal semen.

5 Sperm Antibodies:

this test is done when there is Sperm agglutination (+ve)
we do these tests:

(a) Immuno beads test:

Sample: washed sample to wash seminal plasma.
Reagent: Immunobeads (Polyceramide beads) Coated with IgG, IgA
Reaction: Sperm with antibodies adher to immunobeads
Result: this test is +ve when 50% or more of sperms coated with beads

(b) Mixed Antiglobulin Reaction (MAR)

Sample: Fresh sample not washed.
Reagent: Latix particles coated é IgG, IgA then add to Antihuman Antiserum
Reaction: Sperm with antibodies will adher to Latix particles.
Result: the test is +ve when 50% of sperms coated by latix particles.

NB if agglutination is +ve and sperm antibody is +ve ⟹ Semen-mucus interaction test is needed.

6 Non Sperm cells: (Round cells)

Normall found. they are 2 types:-

(a) Leucocytes:

Normal Range 1 million/mL if it's more than this range it means (infection) ⟹ poor quality of sperms

it can be detected by one of (2) testes:

(1) Peroxidase test
- depend on the peroxidase enzyme in the granules of PMNL
- Cannot detect Leucocyts, Lymphocytes

(2) Peroxidase test depend on Monocolonal Ab to detect Leucocyte-specific-Antigen CD45
- More accurate

(b) Immature spermatogenic cells:

- it may be Round spermatide or spermatocyte or spermatogonia.
- it means defective Spermatogenesis
- they can be stained by → Bryan Leishmon stain
  → Periodic Acid schiff (PAS) for the acrosome.

(c) RBC (d) Epithelial.

NB Pyospermia = Leucocytospermia

pus cells > 5/HPF or > 1million/mL

these Leucocyte produce 3 ROS [Hydrogen peroxide, Superoxide, hydro xyle radical]

which inhibit sperm motility and it's function.

Asthenozoospermia:

- it means motility is less than 32% (a+b) progressive
  or < 40% (a+b+c) progressive, Non progressive.
- Types: ① oligoasthenozoospermia ② Isolated asthenozospermia.
- Causes of isolated asthenozoospermia:-

Un proven Causes	Proven causes
1- Varicocele	1- mistake in collection of sample
2- Epididymal dysfunction	2- Axonemal structure anomalies
3- Nutritional, vit deficiency (vit C, folate, zinc, selenium)	3- Anti-sperm antibody.
4- Genetic Factors (cystic fibrosis, Kartagener's)	4- Infection: Mycoplasma, E.coli, Trichomonas. Rx Culture, Antibiotic
5- Mental Stress.	5- Necrozospermia.
6- Smoking / Alcohol	
7- Exposure to heavy metals	
8- Hormonal imbalance	
9- Chemotherapy.	

- Diagnosis:
  ① history
  ② Examination ← varicocel, urethral discharge (infection)
  ③ Lab examination → Repeated semen analysis
  → Post-massage urethral culture
  → Anti-sperm antibody
  → CASA (when sperm motility < 10%)

- Treatment:

Specific Treatment	Emprical Rx
▸ immotile cilia syndrome → ICSI	- Androgen Replacement
▸ un-explained <10% motility → ICSI	- PDE inhibitor
▸ Varicocel → varicocelectomy	- clomid - tamoxifen
▸ Infection → Culture + Antibiotic	- pentoxyphilline
▸ Antisperm Antibody → Steroid, IVF ICSI	

Advanced Semen Analysis

optional tests

- CASA
- Chemical studies
- Culture studies
- Chromatin studies.

Sperm Function tests

- Sperm mucus interaction
- Sperm Capacitation
- Zona-binding & acrosome reaction
- Sperm-ovum interaction.

[1] CASA = Computer Aided Semen Analysis:

① Semi-automated technique that visulaize and analyze dynamic sperm images through Computer.

② Basic measurments: Concerned with sperm velocity, Kinematic as Follows:

- VCL (Curvilinear velocity) = velocity of the sperm in mm/sec along it's actual path between 2 succesive positions.
- VSL (straight-line velocity) = velocity of the sperm in mm/sec along straight path between it's first position and Last ~~its~~ ~~to~~ position. it measure forward progression.
- Linearity = $\frac{VSL}{VCL}$

③ Advantages: precision and provision of the quantitative data on the sperm Kinematics.

④ Disadvantages: expensive — Complicated — Not standardized imprecise when there is tissue cells or debris.

[2] Chemical studies:

chemical study for markers of accessory sex glands plus ROS

ⓐ Chemical marker for prostate: zinc, citric acid, acid phosphatase, gamma glutamyl transpeptidase

ⓑ " markers of Seminal vesicle: fructose, prostaglandins

ⓒ " " " Epididymis: glycerophosphocholine, L-Carnitin, α-glucosidase.

ⓓ ROS: Reactive oxygen species: metabolites of oxygen produced by sperm, Leucocytes they do oxidative damage of sperm prokins, DNA, Lipids

Sperm can be protected From Ros by

- Enzymatic Antioxidants: Catalase, glutathion peroxidase, Superoxide dismutase
- Non enzymatic antioxidants: vit C, vit E, uric acid

Example of ROS: Nitric oxide, hydrogen peroxide, hydroxyl Radical, Hydroperoxyl Radical → they cause abnormal or immature sperms.

3] Culture Studies:

it is not a routine test. it's done only in pt' with inflammation or infection (cystitis, urethritis)

ex: pt with more than 10 round cell / HPF
or more than 1 million leucocyte / mL.

4] Chromatin studies:

① The normal sperm chromatin is condensed, inactive and don't take any stain

② While the Abnormal sperm has distrubed chromatin → take stain

③ the stains used are: Aniline blue, Acridine orange stain

Sperm function tests:

① Sperm-mucus interaction:

ⓐ in vivo (Post Coital) test.

Aim: to evaluate the sperm function of penetration and servival inside the ovulatory endocervical mucus within 9-24 hours after Coitus

technique: 2 samples are taken by Non lubricated speculum 1st sample from vaginal pool. 2nd sample endocervical

timing: the day of ovulation it should be detected correctly by: Basal body temp., serum Oestrogen, Ultra sound and modified Insler score of cervical mucus as Follow:

① Volume	② Viscosity	③ elasticity	④ Crystallization	⑤ Cellularity
0 = 0 mL	0 = high viscid	0 = thread < 1cm	0 = No Ferning	0 = > 20 WBC/HPF
1 = 0.1 mL	1 = intermediate	1 = 1-4 cm	1 = Atypical ferning	1 = 11-20 WBC/HPF
2 = 0.2 mL	2 = mild	2 = 5-8 cm	2 = 1ry, 2ry Ferning	2 = 1-10 WBC/HPF
3 = 0.3 mL	3 = watery	3 = 9 cm or more	3 = 3ry, 4ry ferning	3 = 0 WBC/HPF

- minima score is 0 and maximum score is 15
- score >10 = good cervical mucus if <10 = unFavorable cervical mucus.

- test results
  - ① vaginal pool sample: if it contains sperms it indicates good semen deposition while if it's free of sperms it indicates loss of semen deposition due to mechanical or Coital Factors. (dissussed later)
  - ② Endocervical sample: if it contains sperms → it exclude any cervical Factors of infertility.
    - if it's free of sperms the test should be repeated.
    - it's called Repeated or Abnormal post coital test.

Causes of poor post coital test:

- ⓐ male Factors → ED, Ejaculatory dysfunction
  - → poor semen quality → ↓ motility, count
- ⓑ Female Factor → mechanical Causes [vaginismus, Vaginal septum, Abnormal cervix]
  - → Abnormal cervical mucus.
- ⓒ Sperm Antibodies.

ⓑ In vitro test

it's done when there is repeated −ve or abnormal post coital test.

Time: the day of ovulation after 1 hour of Coitus

it's done by one of ② methods:

- Slide method: a drop of semen is placed on a slide near to cervical mucus. and we check the ability of sperms for penetration under microscope.
  - it's simple method but not accurate or quantitative.
  - good results means good penetration power, good progressive motility
  - Abnormal results indicates sperm penetration But either immotile or shaking movements → So Antisperm antibody tests should be done.

- Capillary tube method: (Kremer test)
  - Cervical mucus is placed in a capillary tube that is placed with Semen.
  - the sperm migration distance should be at least 4-5 cm.
  - Penetration density should be at least 50 sperm / LPF
  - Duration of Progressive motility should be at least 24 hours

Any other finding indicates → Poor or Negative test.

(2) Sperm Capacitation test:

it can be evaluated in vitro by CASA as Following:

- Semen is washed then incubated in Albumin containing culture media. then examined by CASA.

CASA can detect the hyperactive sperms in motility. cause they have the Following characters:

- high curvilinear velocity (↑ VCL)
- Low Linearity
- ↑ Amplitude of lateral head displacement.

(3) Zona binding and Acrosome reaction.

(a) Zona binding (Hemi zona assay):

- unfertilized oocyte is obtained. and the zona is divided into 2 equal parts by micromanipulator.
- the capicitated sperms of the patient are added to the 1st half
- " " " of the fertile donor " " " " 2nd half
- the sperm binding ability = $\frac{\text{Number of pt bound sperms}}{\text{Donor bound sperms}} \times 100$
- this test is an excellent predictor of fertilization Rate in ART
- there are Zona glycoprotins (ZP_3, ZP_2) responsible for sperm binding

(b) Acrosomal Reaction:

- Detection of acrosomal reaction needs specific staining for acrosome parts
- induction of the reaction by Calcium ionophore
- Normal Fertile semen have: spontaneous acrosome reaction rate < 5 %
  : induced acrosome reaction rate (15-40 %)
- Infertile semen have: higher rate of spontaneous acrosome reaction and Lower rate of induced acrosome reaction.
- this test is indicated in unexplained poor fertilization rate in (IVF) to detect acrosomal defects.

(4) Sperm – Ovum interaction: Zona-Free hamster egg penetration.

- egg of Ramster is induced for ~~hyper~~ super ovulation by hormones then obtained.
- these eggs are treated by hyaluronidase and trypsin in order to remove the layers of Cumulus and Zona pellucida respectively.
- the pt' sperms are incubated with the egg after induction of acrosomal reaction.
- this incubation for 3 hours at 37°C in 5% Co_2
- then the oocyte washed, Fixed, examined for sperm penetration

Normally: 10-30 % of ova are penetrated.
< 10 % penetration defect in fertility.

- Dis advantages: difficult standardization that may lead to False negative result. ie
(pt' with -ve test can fertilize Human oocyte in vivo and in vitro).

Causes of male infertility

1) Pre testicular causes Endocrinal infertility

- Hypothalamic disorders
  - Kallaman syndrome
  - Prader willi s
  - Male anorexia nervosa
- pituitary disorder
- Hyper prolactinemia
  - prolactinoma
  - Craniopharyngioma
- Thyroid disorders
  - Hypothyroidism
  - Hyperthyroidism
- Adrenal disorders
  - hypoadrenalism
  - hyperadrenalism

2) Testicular Causes

- primary testicular and sperm disorder
- testicular artenes disorder (torsion)
- testicular veins disorders (varicocele)

3) Post testicular Causes

- Coital (mechanical) infertility
- obstructive infertility
- Immunological infertility

4) Multi Factorial Causes

- infection
- Neoplasm
- medical causes

[I] Pre testicular causes of infertility
Endocrinal infertility

[a] Hypothalamic disorders: Kallman syndrome, Prader willi syndrome, Male Anorexia nervosa.

⊙ **Kallman syndrome:** X-Linked - Autosomal Recessive syndome. in which there's defect in gene (KALIG-1) which responsible for migration of GnRH neurons From olfactory area to Hypothalamus with Failure of Formation of olfactory bulb Leading to Anosmia [loss of smell]. this pt' have failed puberty and ↓ testicular size, Cleft lip, cleft palate, Colour blindness Cryptoorchism, obesity, micropenis, ↓GnRH, ↓FSH, ↓LH

⊙ **Prader willi syndrome:** Failure of hypothalamus to produce GnRH → Failed puberty. [H30] syndrome: Hypomentia, Hypotonia Hypogonadism, obesity.

⊙ **Male Anorexia nervosa:** which there is ↓ FSH, ↓LH, ↓ Testosterone the condition improve by Androgenic therapy or weight gain.

⊙ Treatment of hypothalamic disorders:

▸ aim of R → during puberty: to improve, development of sex characters, organs.
→ After marriage: initiation of spermatogenesis, fertility.

▸ Types of R → Pulsatile GnRH therapy: pulsatile doses of 5 - 20 µg in pulse/120 min / Subcutaneously.

→ Combined therapy HCG + HMG

HCG (Human chorionic gonadotropins) — Pregnyl - epifasi - chorionon — 1000 - 3000 IU twice weekly /IM

HMG (Human Menopausal gonadotropin) — Humegon, pergonal, Menogon — 150 IU 3time/week /IM

▸ the therapy should be Continued till the sperms appears in the semen and/or pregnancy occurs.

[b] Pituitary disorders: hyperprolactinemia / other pituitary disorders.

① Hyperprolactinemia.

- Normal serum prolactin is 15-20 ng/mL it's controlled by balance bet
  1. Stimulation: by Prolactin Releasing Factors
  2. Inhibition: by Prolactin inhibiting Factors (dopamine) secreted by Hypothalamus and transported to pituitary gland
- Prolactin may increase physiologically: during sleep, stress, Exercise.

Causes:

1- Prolactinoma: Prolactin secreting tumours: Micro prolactinoma < 1 cm / Macroprolactinoma > 1 cm → proliferation, destruction of the surrounding structures (optic nerve)
   - Serum prolactin > 100 ng/mL
   - MEN syndrome (Multiple endocrine Neoplasia): prolactinoma + Pancreatic + Parathyroid

2- Craniopharyngioma: Tumour between the 2 lobes of pituitary Lead to Compression on pituitary stalk → interruption of inhibition of dopamine secreted by hypothalamus → ↑ prolactin.

3- thyroid disorders: Hypothyroidism → ↑ TRF (Thyrotropin Releasing Factor) which is stimulant of prolactin secretion.

4- hepatic / Renal disorders: ↓ metabolic clearance of prolactin.

5- Drugs: Tricyclic antidepressant TCA, Phenothiazine, ∝ methyl dopa, Oestrogen.

- Effect of hyperprolactinemia on infertility:
  ① Hyperprolactinemia → inhibition of pulsatile GnRH Release → ↓ FSH, ↓ LH, ↓ testosterone, defective spermatogenesis.
  ② prolactinomas → direct effect on pituitary cells → ↓ FSH, ↓ LH.
- Diagnosis: C/P: headache, visual field disturbance, Gynecomastia ↓ desire, ED, Retrograde ejaculation.
  Lab: Hormonal: ↑ s. prolactin, ↓ FSH, ↓ LH, ↓ testosterone.
  Semen: ↓ semen parameters.
  MRI, CT: in micro prolactinomas.

Treatment:

① Bromocriptine (Parodel): Dopamine agonist.
it is a hypotensive drug so the dose is increased gradually start by ½ Tab (1.25 mg) once at night then ↑ to 3 tabelets per day 7.5 mg.
S.E: Hypotension, Nausea, Dizziness, Nasal stuffness, Conistipation.

② Cabergoline (dostinex): Selective dopamine Agonist, potent, well toleratad. Duration of action may long for 3 weeks.
dose 0.3–1 mg it's the drug of choice

② Other pituitary disorders.

- Generalized pituitary dysfunction: due to irradiation, infiltration of TB, Sarcoidosis, hemochromatosis
- Isolated gonadotropins deficiency: As in cases with ↓ LH, FSH.
"Fertile eunuch syndrome" = selective gonadotropins deficiency of LH in which the pt' may have spermatogenic activity and may be fertile but the amount of LH is too small and not sufficient for complete derelopment of sexual characters → lead to Eunuchoidal Features (tall stature, Gynecomastia, obesity, Small, Firm testis)

Treatment of these ② disease is Androgenic Replacement therapy as hypothalamic disorders.

[c] Thyroid disorders:

[1] Hyper thyroidism : ↑ T_3, ↑ T_4, ↓ TSH

this lead to ↑ SHBG (sex hormone binding globulin) which lead to ↓ Free testosterone while total testosterone is normal.

- ED is due to ↑ aromatization of testosterone to Oestrogen → ↓ desire, Gynecomastia → ED
- Rf of the thyroid problem. ~~the~~ (NB) Androgen Rx is not effective.

[2] Hypo thyroidism: ↓ T_3, ↓ T_4 and ↑ TSH

this lead to ↑ TRH (thyrotropin releasing hormone) → ↑ prolactin.

[d] Adrenal disorders:

[1] Hyper adrenalism:

- ↑ Cortisol → Cushing disease [moon Face, Truncal obesity, ↓ desire, ED]
- ↑ Cortisol has direct effect on pituitary gland → pituitary dysfunction → ↑ prolactin → infertility
- ↑ Cortisole has direct effect on testis → testicular dysfunction.

Rf of the cause of increased cortisol level

[2] Hypo adrenalism:

adrenal insufficiency lead to generalized weakness, fatigue, hypotension → Abnormal sexual function → Rapid loss of 2ry sex Charecters.

Diagnosis of Endocrinal Infertility

[1] History

of sexual development, maturation, Androgenic or Anti androgenic drugs

[2] Examination: for

Abnormal virilization, eunuchoidal Features, Gynecomastia, Small testis (Less than 3-5 cm in diameter).

[3] Semen: Azoospermia, oligozoospermia, hypospermia:

hypospermia → Low seminal fluid volume due to

* Retrograde ejaculation
* Congenital bilateral absence of Vas.
* Ejaculatory duct obstruction
* 1ry, 2ry hypogonadism.

[4] Hormonal profile:

(A) FSH ↑ FSH, ↑ LH, testicular Failure → hypergonadotrophic hypogonadism

↓ FSH, ↓ LH, ↓ testosterone → Hypogonadotrophic hypogonadism

◎ (Normal FSH, Normal testicular size + Azoospermia → Obstruction
↳ Germ cell arrest

(B) LH, testosterone

(C) Prolactin, OEstradiole: in pt' with ↓desire, ED, Gynecomastia.

(D)

GnRh test: evaluate the function of pituitary to secret FSH, LH

HCG test: differentiate between Absence and maldescent of testis.

NB Free testosterone is more accurate than total testosterone.

◎ ↑ SHBG → ↓ Free testosterone (Hyperthyroidism, hepatic cirrhosis)

◎ ↓ SHBG → ↑ Free testosterone. (Hypothyroidism, Obesity).

[2] Testicular Causes of male infertility

1ry testicular and sperm disorder	testicular arteries disorders (Torsion)	testicular veins disorders (Varicocele)

1ry testicular disorder
- cryptorchidism
- Germ cell arrest
- Germ cell aplasia
- Klinefelter. syndrome
- Noonan Syndrome.
- Myotonic dystrophy.

1ry Sperm disorders.
- Globozoospermia
- Immotile cilia syndrome.

Primary testicular disorders.

it means Congenital or Chromosomal Cause.

NB ⊛ 1ry or hypergonadotrophic hypogonadism → ↑ FSH, ↑ LH.
⊛ 2ry or hypogonadotrophic hypogonadism → ↓ FSH, ↓ LH.

[1] Cryptorchidism:

means = "hidden testis" ie Not palpable in scrotum.

it may be in The Form of:
① Anorchia ② undescended testis ③ Retractile testis ④ Ectopic testis

ⓐ Anorchia:

⊙ Normally the testis ~~desc~~ start develo at the 8th week intrauterine life
⊙ if there is Loss of testis or reggression or disappearance due to
- Loss of vascular supply of the testis intra uterine
- Torsion, Maternal infection, trauma → loss of testis → Anorchia

⊙ According to the time of reggresion the baby will shows:
- if reggression **Before** 8th ~~week~~ → Female genitalia (XY)
- " " between 8th – 10th weeks → baby with Ambiguous genitalia
- " " between 12 & 14th week → the baby will have normal genitalia (Penis, scrotum) but with No testis.

(b) Undescended testis:

- the testis is arrested at a point during its course due to genetic, mechanical, hormonal factors.
  - Retroperitoneal
  - Intra-abdominal
  - Inguinal
- it may be found in one of it's course.

Complications of undescended testis:

- **Infertility:**
  - the bilateral cases more infertile than unilateral cases.
  - the higher testicular postion the higher (sever) testicular dysfunction
  - the Absence of germ cells in inguinal testis is 20–40% while Absence in intra abdominal testis is 90%
  - the pt' has: ↓ testicular volume, impaired semen parameters
    - ↑ FSH.
    - May have sertoli cell only syndrome while Leydig cell are normal.
- **Malignancy:** even after orchiopexy or unilateral cases the pt has higher incidence of malignancy.
- ↑ incidence of Torsion, Trauma, and Hernia.

(c) Retractile testis:

- that means the testis is easily withdrow from the scrotum to a higher position along it's normal course of descent.
- it's due to strong cremastric Reflex.
- incidense rate 4%
- Abnormal semen parameters or may be ↑ FSH

(d) Ectopic testis:

- the testis are found outside it's normal course of descent.
- it may be found in superficial inguinal pouch or perineum, penile shaft, or Antero-medial aspect of the thigh
- Ectopic testis have higher incidence of Trauma
- Infertility rate is not known yet
- No higher malignancy as undescended test.

diagnosis of Cryptorchidism: clinical Examination / Lab Examination / other diagnostic procedures.

① **Examination:** should be in ③ different positions.

- **Supine position:** ▷ ectopic testis can be felt.
  ▷ Inguinal undescended testis can be felt at ext. ring and can be pulled up.
- **Sitting position (squatting):** ▷ to eliminate the cremastric reflex
  ▷ to help to pull retractile testis into scrotum but undescended testis can't be pulled.
  ▷ the skin of hemi scrotum is well developed in Retractile testis but not in Undescended
- **Standing position:** help to detect the inguinal hernia occuring with undescended testis.

② **Lab**

- Semen: may show oligoathenozoospermia or Azoospermia
- Hormonal and chromosonal study: to detect associated syndromes: Down ṣ, prader willi ṣ, Kallman ṣ, intersex.
- Human Chorionic gonadotropin (HCG) test: it's given (1000–2000 IU) / 3 times / weekly.
  in cases of undescended testis → ↑ testosterone Level
  " " Anorchia → No effect.

③ **others:**

- MRI followed by CT and U/S: the diagnostic imaging of choice but difficult in chidren intra abdominal testis.
- Diagnostic laparoscopy: useful but not a Righter intraabdinal testis.
- Diagnostic laparotomy: Larg abdominal incision is the best.

Treatment of cryptorchism

[A] Age of Treatment:

Should be after 1 year age to allow spontaneous descent and before the age of 2 years to prevent spermatogenic damage.

[B] Medical Treatment: it's helpful especially in Non Complicated Retractile testis rather than undescended or Ectopic testis

- HCG (IM): 0–2 years ⟶ 250 IU/twice weekly/5 weeks
  2–5 years ⟶ 500 IU/ " " / "
  5–10 years ⟶ 1000 IU/ " " / "
  Success Rate is 30–40 %
- Intranasal GnRH: NaFarelin (synarel spray) / Busurelin (Suprefact) 3 times daily for 4 weeks.
  success Rate is 0 — 78 %

[C] Surgical Treatment:

indications:

- Failed medical R/
- Complicated cases
- Ectopic testis.

3 types of operations:

(1) Immediate Orchidopexy: though laparoscope or open surgery: the testis are pulled and fixed in scrotum by stitches.
: it's indicated in:
- Enough Length of testicular vessels as in ectopic or some Cases of undescended testis.

(2) Two stages orchidopexy: this is done in cases of short testicular vesseles @ the testicular artery is Ligated ⟶ it lead to Enlargment, elongation of Collaterals.
2nd stage: Six month later the testicular vesseles are divided and the testis is brought down by the pedicle of new collateral vessels.

(3) Orchidoectomy: it's done if the testis are grossly abnormal or couldn't be pulled due to sever shortness of vesseles or the pt is postpubertal or the testis Loss it's spermatogenic function orchidectomy is done to avoid high risk malignancy.

[2] Germ cell Arrest (Spermatogenic arrest)

- By germ cell arrest means interuption of spermatogenesis at any Level. From spermatogonia to sperm Formation.
  Spermatogonia → 1ry spermatocyte → 2ry spermatocyte → Round spermatid → Sperm
- NB Hypospermatogenesis means Normal spermatogenesis but Reduced in number
- C/P : ⊙ Normal testicular volume
  - ⊙ abnormal semen parameters : Azoospermia, (⊙AT) in partial arrest.
  - ⊙ ↑FSH, Normal LH, Normal testosterone.
- Causes: unKnown but may be related to 2 genes:
  1. AZF azoospermia Factor: Found in Y chromosome
     it's deletion lead to spermatogenic arrest
  2. DAZ deleted in Azoospermia : lead to arrest and azoospermia.
- Diagnosis : testicular biopsy.
- Treatment ⊙ Non specific ℞ ⊙ ICSI in some Cases of spermatogenic foci

[3] Germ Cell Aplasia — Sertoli Cell only syndrome

Abscence of germ cells with pereservation of sertoli cell and Leydig cell.
Diagnosed by testicular biopsy
Causes (Congenital) Failure of migration of germ cells to the gonadal ridgs
lead to testicular aleroid of spermatogenesis
C/P and Treat ment the same as Germ cell Arrest.

[4] Noonan Syndrome

⊙ Inherited Autosomal dominant syndrome. ⊙ 46 XY
⊙ Similar to Turner Syndrome in Females (45 X/O) short stature, ptosis, Low set ears, webbed neck, CVS anomalies, ↑FSH undescended testis, defect spermatogenesis but some may be Fertile.

[5] Myotonic Dystrophy

Autosomal dominant with abnormal protein Kinase gene.

- it's characterized by myotonia (delayed muscle relaxation after Contraction).
- the pt' have: baldness, Cataract, Cardiac anomalies, testicular atrophy with sever tubular sclerosis.

[6] Kline Felter Syndrome: the most common male Hypogonadism.

- Any phenotypic male with 2 or more X chromosomes plus at least one Y chromosome. eg: 47 XXY → the most common.
  (48 XXY)(48 XXYY)(47 XXy / 46 XY) → mosaicism.
- Pathology:
  - testis: → Shows → Fibrosis, hyalinization of Seminiferous tubules
    So the testis are small, there is Azoospermia.
    mosaicism: show Normal spermatogenesis with oligoazoospermia
  - Leydig Cell: Normal or hypertrophic But with impaired function due to Abnormal mitochondria and Endoplasmic Reticulum.
    the impaired function of Leydig cell will lead to:
    1- ↓ testosterone → delayed puberty.
    2- ↑ LH → testicular fibrosis → small testis.
    3- ↑ Oestrogen → Gynecomastia.
- Diagnosis: ▸ History of delayed puberty, infertility, ↓ desire, ED.
  ▸ Examination: Local: → Firm, small testis Less than 4 mL
  General examination: Eunuchoid or hypogonadal features:
  - disturbed body propotions ie the span > hight
    span is distance bet Full stretched arms.
  - Lower body segment (distance From sde to pubis) > upper body segment (From pubis to head). due to delay fusion of long bone epiphysis → tandog
  - Gynecomastia. with higher incidence of breast Cancer.
  - ↓ muscle strength, Obesity, Varicose veins → (lead to) Leg ulcers.

▸ Investigations:
- Semen: Azoospermia or oligoazoospermia in mosaicism.
- Biopsy: testis are Fibrosis, hyalinization.
- chromosomal studies: (Karyotyping) Extra X chromosome.
  OR ← Extra Barr body (inactivated X chromosome)

Treatment of Kline felter syndrome:

① Androgen Replacement therapy for ↑ muscle strength, desire, ED
② Gynecomastia ⟶ Mastectomy
③ Infertility ⟶ TESE for ICSI in mosacism.

Try sperm disorders

[1] Immotite Cilia Syndrome: Ciliary DysKinesia Syndrome.

- Characterized by many anomalies of the sperm tail so the sperm is non motile but they are alive.
- these anomalies include: Defective dynein arms
  Defective Radial spokes
  Dislocation of microtubules.
- the ciliated epithelium in the body is Also affected.
  - nose ⟶ ch-rhinitis
  - Ear ⟶ ch. otitis media.
  - Sinus ⟶ ch- sinusitis
  - bronchi ⟶ Ch- bronchitis.
- Diagnosis ⟶ Electron microscope
- Treatment ⟶ ICSI

[2] Globozoospermia: Round head Syndrome.

the Head is rounded because the Golgi apparatus is not transformed into Acrosome needed For Fertilization.

Diagnosis ⟶ Electron microscope
Treatment ⟶ ICSI.

Remember: testicular causes of Male infertility
1. 1ry testicular, sperm disorders.
2. Testicular arteries disorder (Torsion)
3. Testicular veins disorders (Varicocele)

[2] Testicular arteries disorders

Testicular Torsion

Def: Rotation of the testis around its Long axis due to twisting of spermatic cord.

Types:

① Neonatal (Extravaginal) Torsion: occurs in the first 10 days after birth. due to Tunica vaginalis is not yet Fixed Leading to Free movement of the testis in scrotum → Torsion.

② Childhood, Adulthood [Intravaginal) Torsion: The tunica vaginalis is fixed and the testis can move Freely inside the tunica vaginalis due to decrease fixation of T. vaginalis to the posterior wall of Testis OR due to horizontal Lie of testis inside The Tunica vaginalis.

effect of Testicular Torsion:

- occlusion of testicular artery → Ischemia → Necrosis.
- affection of the Contralateral testis.

C/P:

- In horizontal Lie testis the pt' suffers from Recurrent attacks of pain
- The classical C/P is Sever unilateral scrotal pain with Lower abdominal pain + Nausea + vomiting.

D.D: ⊙Traumatic: haematocele, strangulated hernia ⊙Inflammtory: Epididymo-orchitis ⊙Neoplastic

Investigations: Colour doppler U/S → ↓ blood Flow.

Treatment: Surgical exploration is the treatment after correction of

- if the testis becomes Red → it's viable → orchiopexy (fixation of testis in scrotum by 3 sutures.
- If the testis cyanosed → Orchiectomy.

	Testicular Torsion	Epididymoorchitis
Def	Rotation of the testis around its long axis due to twisting of spermatic cord.	inflammation of the epididymis + testis
Age onset	usually Neonatal, adolescence sudden	mainly sexually active men. Acute
Constitutional symptoms	Absent	fever, headache, malaise
Testis	Retracted upward -ve -ve Free	go down word is 2ry complication. posteriorly in T.B pyuria
Colour doppler	↓ Blood Flow	↑ Blood Flow
Elevation of scrotum	↑ pain (prehn's sign)	↓ Pain
Cremastric Reflex	Loss	+ve
Treatment	Immediate surgical exploration then orchiopexy or orchiectomy	Bed rest NSAID Antibiotics Rx of Complications eg Hydrocelectomy

Continue testicular causes of male infertility

[3] Testicular veins disorders

- Varicocele -

Defenition:

Varicocele means [dilatation, elongation, tortuosity, tickening] of scrotal part of pampiniform plexus of veins.

Remember: Testicular venous drainage
- Ant. group:- testicular group
- middle group → vas group
- Post. group → cremastric group.

Eithology: [primary, secondary]

⊙ **Primary:**
- Long, Free course of testicular veins in the intraperitoneal space without supporting muscles. [pump → Reflux → varicosity]
- Long standing Reflux in testicular vein [Reflux → varicosity of cremastric and vas veins]
- Abscent of valves or (incompetent).

⊙ **Secondary:** Rare
- due to Compression on testicular veins in the retropretoneal area by retropretoneal tumours or renal tumours.

Why the Left side varicocel is more common than Right side??

1- Lt testicular veins drain by right angle in Lt renal vein and that makes slow blood Flow → stagnation → varicocel
But the Rt testicular vein drain by oblique angle in IVC
2- Lt testicular vein (8-10cm) longer than Rt testicular vein → ↑ pressure in the Lt vein in upright position.
3- Abscence or incompetent valves are more in Lt side
4- Lt Renal vein compression between Aorta and superior mesentric artery (nut craker phenomenen)

Diagnosis of varicocele

- Doppler
- Duplex U/S
- venography
- Thermography, thermometry
- CT scan, MRI
- lab diagnosis:-
  - Hormonal profile: FSH, LH, testosterone, GnRH stimulation test.
  - Inhibin B., Transferrin.

Varicelectomy is the Treatment of choice.

indication of varicelectomy:

1- infertility: infertile men with no other causes of infertility
2- Semen analysis: pt with varicocele with abnormal semen Parameters.
3- Symptomatic varicocele:
persistant testicular pain - inguinal pain
4- pediatric / adolescent men:
if there's persistant pain or gross testicular damage or gross reduction of testicular size or failure of growth during repeated Follow up.
5- Secondary infertility:
when there's other associated Factors causing infertility

Varicocele and infertility

Mechanism of varicocele in infertility:-

(1) Hyperthermia: caused by varicocele leads to
- testicular dysfunction
- direct effect on germ cell
- Altered metabolism → ↑ apoptosis
- Sertoli cell dysfunction
- ↑ arterio-venous shunt → ↓ activity of the enzymes involved in DNA synthesis and ↓ O_2 and ↓ nutrients to the testis.

② Reflux of renal metabolities:

- Lt Renal vein ($Na + K^+ +$ urea + PG) → impair spermatogenesis
- Lt Adrenal vein (catecholamines) → Testicular vasoconstriction + testicular dysfunction.

③ Venous stagnation:

it will Lead to:

- ↓ O_2 (Hypoxia)
- ↑ Co_2 (Hypercapnia)

→ affect spermatogenesis

- ↑ ROS (reactive O_2 species) that lead to:
  - cellular damage by means Lipid peroxidation → ↓ sperm motility, ↓ viability, ↓ Capacitation, ↓ acrosome reaction, ↓ sperm-ovum Binding

④ Apoptosis:

Cause of the prescence of heavy metals (toxic agent) eg:
Cadmium → Lead to cellular apoptosis.

⑤ Enzymatic function: (eg) topoisomerase I, DNA polymerase
these enzymes have less activity in pt' with varicocele.

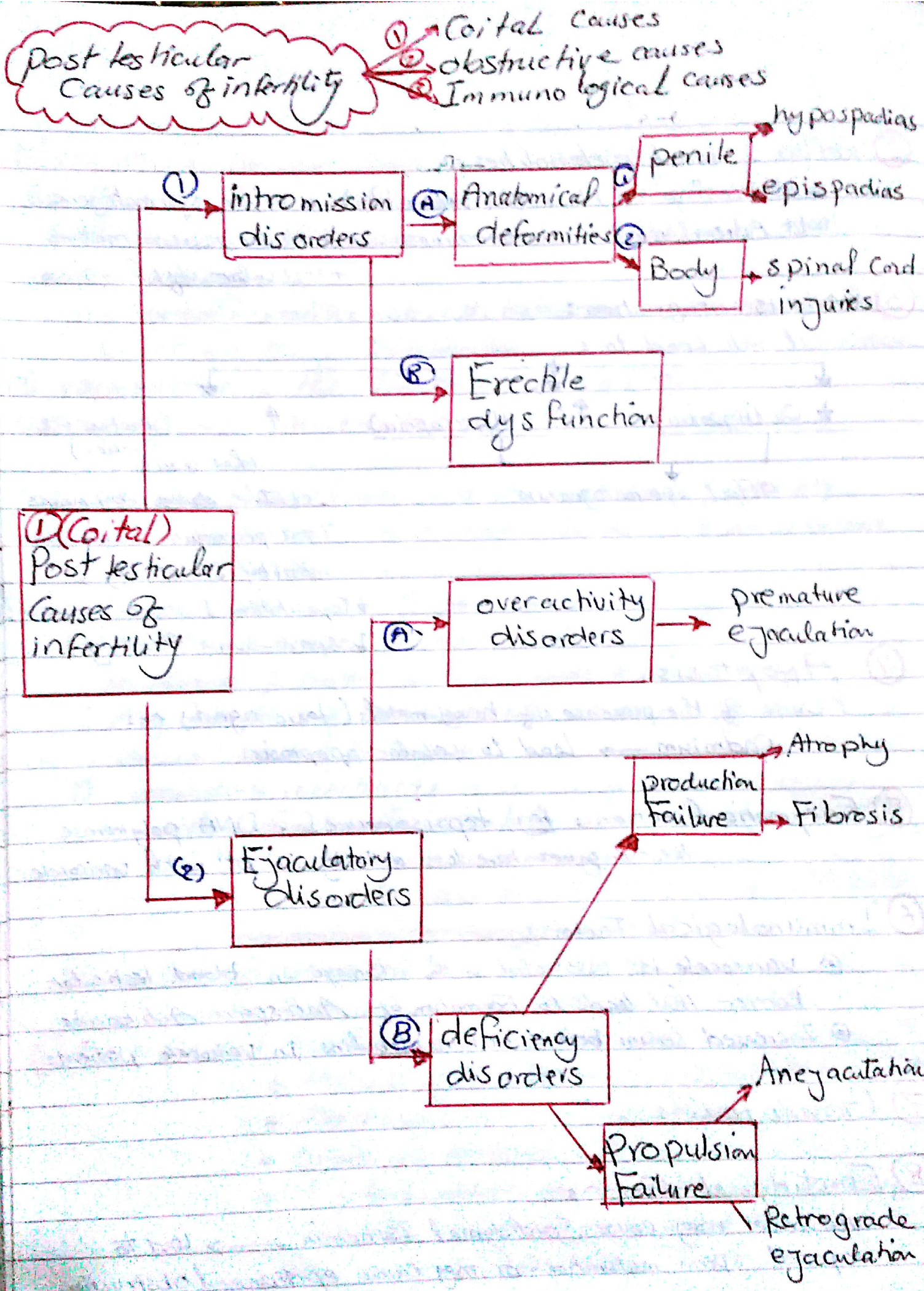
⑥ Immunological Factors:

- varicocele is associated with damage in blood testicular barrier that leads to Formation of Antisperm Antibodies
- Increased serum bound immunoglobulins in varicocele patients

⑦ Gonadotoxins.

⑧ Epididymal Factor:

varicocel may cause Epididymal Ischemia → Lead to impaired sperm maturation or may cause epididymal obstruction.



Coital causes of Post testicular causes of infertility

(1) Intromission disorders:

A) Anatomical deformities:

① Penil deformities:

- Hypospadias: Congenital anomaly in which the penil meatus is found under the surface of penis lead to Failure of semen deposition in vagina → infertility
- Epispadias: penile meatus on dorsal surface

R/ of penil deformities → IUI (intrauterine insemination).

② Body deformities: Spinal cord injuries → unsuccessful intercourse and may associated with ED → infertility

R/ IUI

B) Erectile Dys function: "see the chapter of ED."

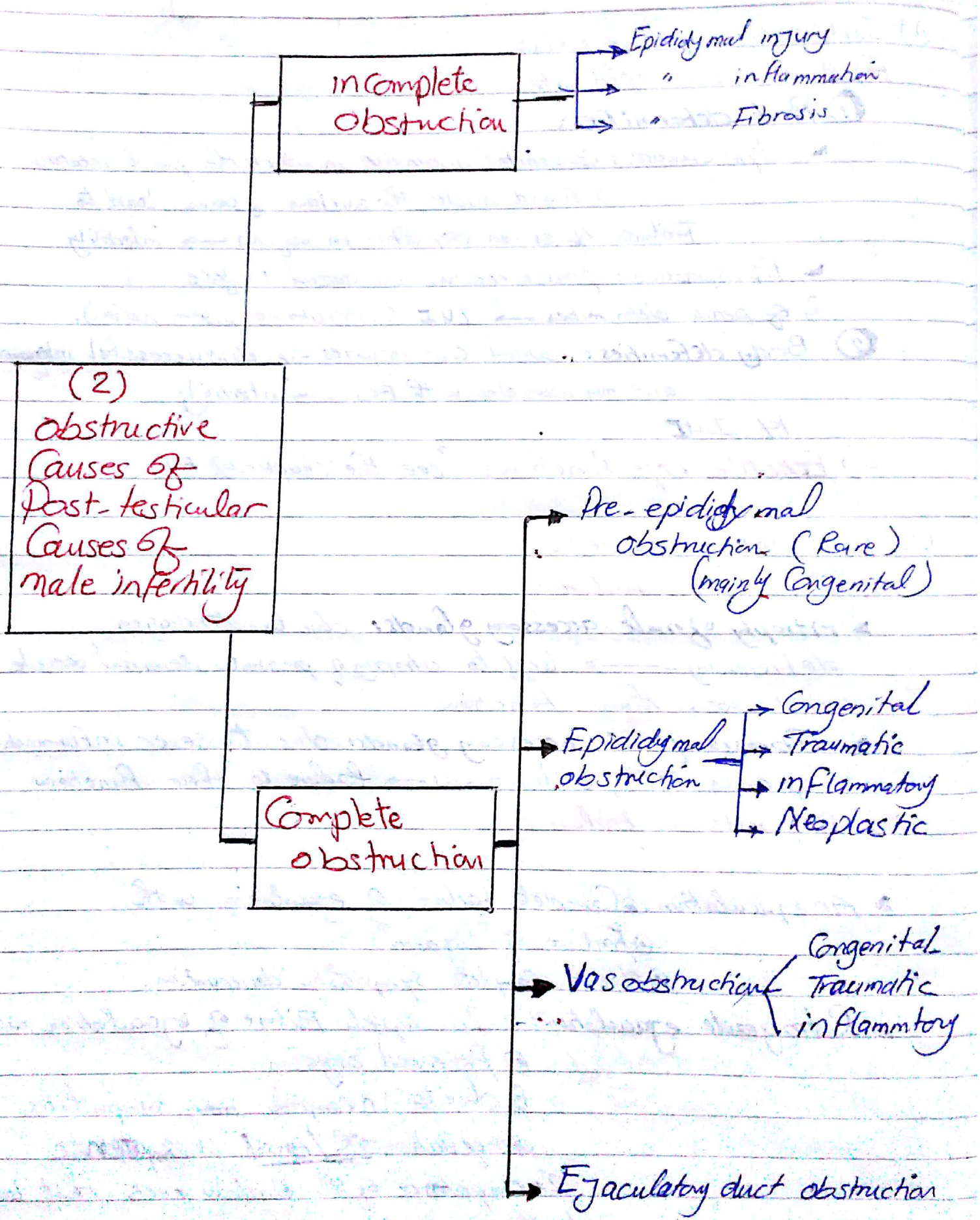
(2) Ejaculatory disorders:

A) Production failure:

- Atrophy of male accessory glands: due to Androgen deficiency → lead to atrophy of prostates, seminal vesicle and loss their function
- Fibrosis of male accessory glands: due to sever inflammation espicially TB, bilharziasis → failure to their functions

B) propulsion failure:

- Anejaculation: ⊙ Complete failure of ejaculation with
  ⊙ failure of orgasm
  ⊙ due to complete sympathetic denervation.
- Retrograde ejaculation: ⊙ Incomplete Failure of ejaculation with
  ⊙ Preserved orgasm
  ⊙ due to incomplete sympathetic denervation SR/Andr in competence
  Incompetence of the bladder neck that lead to retrograde direction of ejaculate into the bladder.



Obstructive infertility

incidence : 3 - 13.6 % of andrological patients.
depend on the site, the nature, and the duration of obstruction
Causes:

(1) Incomplete obstruction.

- good Quality of spermatogenesis and poverty of sperms in the ejaculate suggests incomplete obstruction
- mechanism:
  epididymal injury of any cause → Extravasation of sperms and → inflammation + granuloma formation → Fibrosis of epididymal duct.
- Some sperms may leak through a narrow channel this is manifested by oligozoospermia
- Diagnosis: semen : oligozoospermia
  Hormonal profile : Normal
  Testicular biopsy: Normal spermatogenesis.

(2) Complete obstruction.

(A) Pre epididymal obstruction:

- rare and mainly Congenital
- Site : obstruction in Rete ridges or ~~the~~ vasa efferentia
- Treatment: RETA (rete testis aspiration) Followed by ICSI.

(B) Epididymal obstruction:

[I] Congenital:

- Total absence of the tail of epididymis
- Failure of the union between the head of epididymis with body and tail of epididymis or Failure of union between epididymis and vas deferens.
- Aplasia (Abscence) of the body or tail of epididymis or Vas deferens
- Young Syndrome:
  ① obstruction of epididymis and vas due to abnormal thick secretions
  ② Pulmonary disorders (bronchiectasis). ③ Sinusitis.

[2] Traumatic:

- Accidental trauma (Rare) (scrotal)
- Iatrogenic: during operation: testicular biopsy or Varicocelectomy

[3] Inflammatory:

- Acute or subacute epididymitis → partial obstruction → oligozoospermia
- Clinically: epididymis is: soft, enlarged, swollen, tender
  may persist for 2 years or more
  Response to Antibiotics, NSAIDs.

[4] Neoplastic: → Cystic tumour
→ Non cystic Tumour: Adenoma, Teratoma, metastatic tumour.
→ Von Hipple Lindau syndrome:
(epididymal tumour + Cerebellar an Retinal hemangioblastomas)

(C) Vasal obstruction:

[1] Congenital:

* 1-2 % of malinfertility
* the testis and the head of epididymis are present because the have different embryonic origin (mesonephric tubules) while the vas, seminal veside, ejaculatory duct arise from mesonephric duct.
* Congenital anomalies of vas may be unilateral or Bilateral, partial or ~~in~~complete
* The epididymis may be normal or partially aplastic
* there may be some missing junctions bet epididymis, vas

* Congenital anomalies associated with Absence of vas:

① Anomalies of Respiratory, digestive system (cystic fibrosis)
AD with CFTR gene (Cystic fibrosis Transmembrane Conductase regulator gene) characterized by ⊙ infertile ⊙ Bilateral absence of vas ⊙ cystic fibrosis of lung, Pancreas).

② Anomalies of urinary tract:-

⊙ AR disorder ⊙ characterized by: unilateral Absence of vas + Ipsilateral absence or deformity in the Kidney, ureter, urinary bladder

Characteristic semen picture in Congenital absence of vas:

NB Absence of vas + S.vesicle + ejaculatory duct

1- low semen volume Cause the seminal vesicle produce 65 % of ejaculation volume
2- Absence of semen Coagulation (Coagulating enzymes from S.vesicle)
3- Absence of fructose, PGs (secreted from S.vesicle).
4- Azoospermia
5- Absence of (L-carinitine, glucosidase, glycerophosphoryl choline) epididymal products.

NB there is difference in the semen picture in absence of vas and vasal obstruction because the seminal vesicle is present. So:

⊛ Normal volume of semen ⊛ Azoospermia
⊛ Viscid, Normal pH, Normal Fructose, PGs
⊛ Absence of epididymal, testicular markers.

[2] Traumatic:

▲ Iatrogenic: during inguinal herniotomy more in infant
↳ vasography
▲ Vasectomy: ~~premature ster~~ preminant sterilization

[3] Inflammatory: Causes as epididymitis.
urinary tract: E.coli - Pseudomans.
sexually transmitted: Nessieria gonorrhea, Chlamydia.
Blood borne: [TB. Bilharziasis, Filiriasis, Leprosy, syphilis]

[4] Ejaculatory duct obstruction:

Semen picture is the same of Absence of vas but the vas is felt clinically. Causes:

① Congenital → Mullerian duct cyst.
② Acquired → Traumatic: Transurethral surgery, long term catheter
↳ inflammatory: chronic prostatitis (Fibrosing, Scarring)

✱ Diagnosis of male duct obstruction :-

① History : of infertility, with sever azoospermia while testicular biopsy shows normal spermatogenesis.
② Semen : Incomplete obstruction → Severe oligoospermia < 10 million/mL
Complete obstruction → Azoospermia
③ testicular biopsy : Normal spermatogenesis
④ Hormonal study Normal
⑤ Vasography : (Radiography for visualization of vasal lumen by injection of dye)
useful in diagnosis, detection the site of obstruction
⑥ Trans-rectal U/S : to diagnose ejaculatory duct obstruction.
⑦ Examination : local → for epididymal, vasal anomalies.
General → for young syndrome (bronchiectasis, sinusitis, epididymal obstruction)

Treatment of male duct obstruction

Preventive R/
- Proper treatment of genital tract infections to Avoid Late fibrosis and obstruction.
- Proper pelvic surgical technique to avoid iatrogenic causes.

(ART)
indications :
* Failed surgical treatment
* Impossible surgical R/
eg: bilat absent of vas
* PETA or TESA → Followed by ICSI.

Surgical Treatment.
(1) Epididymovasostomy :
surgical anastomosis between epididymis and vas.
(2) Vasovasostomy :
surgical correction for vasal obstruction
(3) Surgical operation for ejaculatory duct obstruction :-
Endoscopic trans urethral incision or deroofing of the cyst that occlude the ejaculatory duct.

(3) Immunological infertility

- it means infertility caused by the production of Antisperm Antibodies
- physiology of immunological protection of sperms:-

1- Sperm Antigens:

the sperms are not present during the embryological development when the immune system establish tolerance to self antigen, Accordingly, the sperm specific antigens that are formed only after puberty are received as a Foreign Antigens by the immune system.

examples of sperm antigens:

(1) Fertilization Antigen 1 (FA-1) → regulate sperm-zona pellucida interaction
(2) Creatinine phosphokinase, Lactate dehydrogenase → Regulation of spermatogenesis

2- Protective mechanisms against sperm Antigens:

1- immunoseparation helped by (Blood testicular barrier) which separate the Antigenic Sperms from the blood and Lymphatic vesseles that contain Lymphocytes and antibodies.

2- Immunosuppression: Although there are tight junctions between Sertoli cells there are some gaps that allow passage of sperm Antigens into the circulation and in the same time allow the passage of some molecules and lymphocytes into the seminiferous tubules and the epididymis
the leakage of sperm antigen to the circulation will lead to immunosuppression or desentization of immune system through activation of T suppressor cells.

Pathology of immunological Reactions of the sperms:-

A) Causes of production of Antisperm Antibody:

- the main cause is disturbed blood testicular barrier that will lead to abnormal comunication between the reproductive system and immune system.
- other cause is defective immunosuppresion.
- this may occur due to congenital, traumatic, inflammatory and neoplastic causes:-

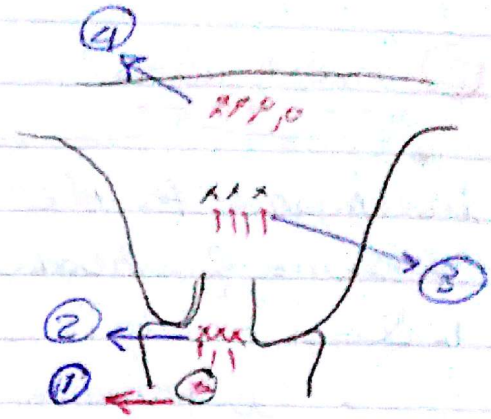
- Congenital
  - Congenital obstruction of genital ducts
  - Cryptorchidism
  - Varicocele.
- Traumatic
  - Iatrogenic trauma durig testicular biopsy or vasectomy
  - Non Iatrogenic trauma → trauma – Torsion
- Inflammatory → Epididymo-orchitis or prostatitis.
- Neoplastic
- Idiopathic
- Homosexuality:→ erosion of rectal mucosa

B) Effects of Antisperm Antibodies:

- Types of Antibodys
  - Ig G → produced in genital tract
  - Ig A → " " + inhibition of sperm cervical mucus penetration
  - Ig M → large molecule limited to serum only.
- sites of Antibodies
  - Male: Serum or Semen
  - Female: Serum or Cervical mucus.

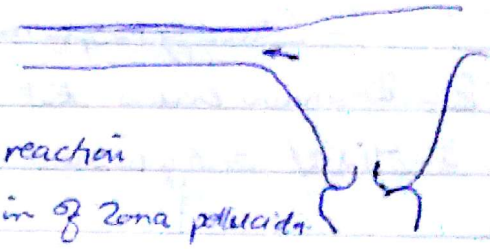
NB the presence of the Antibodies in the serum of male and/or female have no clinical significance.

Actions of Antibodies



(a) sperm transport:

1- Clumping and agglutination in seminal plasma
2- Inhibition of migration through cervical mucus
3- " of progression through the uterus
4- destruction of sperms by complement activation in the uterus.



(b) Sperm ovum interaction:

1- inhibition of sperm capacitation and acrosomal reaction
2- inhibition of sperm attatchment, binding, penetration of zona pellucida
3- inhibition of sperm fusion with oocyte plasma membrane
4- inhibition of sperm activation and pronuclear Formation

(c) Embryo-development:

1- Inhibition of cleavage of Fertilized ovum
2- Direct action against developing embryo.

Diagnosis of Immunological Infertility

(1) indications:

- Agglutination, clumping of sperms in semen.
- Atheno zoospermia
- Leucocytospermia
- Sperm shaking — in sperm cervical mucus Contact testing.
- Sperm poor penetration → of the mucus in post Coital test.
- Unexplained infertility or recurrent abortion with normal semen analysis
- Befor Vaso vaso stomy
  (ex: Leakage of sperm into circulation → Sperm granuloma)

② investigations

Investigation for the presence of antibodies

1- Semen analysis show:
- agglutination
- Asthenozoospermia
- Leucocytospermia

2- Immuno beads test

3- Mixed antiglobulin Reaction

investigations for the effect of antibodies.

1- Sperm mucus interaction
2- Sperm Capacitation
3- Zona-binding and acrosomal reaction.

See the chapter of Semen analysis

Treatment of immunological infertility

⊙ **Preventive Rx:**

early detection and treatment of Causes of immunological infertility eg: varicocele, infection, ... etc

⊙ **Curative Rx:**

Immunosuppresion in ② regimens:

High dose Cyclic therapy

100 mg methyl prednisolone/day for 7 days every month for 3 months.

intermediate dose Continous therapy

40 mg/day/9 month is better than high dose

⊙ S.E of both regimens: gastric complications, salt/water retention diabetes, mood changes, Aseptic nerosis of the hips.

⊙ **Assisted Reproductive technology (ART)**

⊙ IUI: indicated in (Abnormal sperm mucus interaction).

- Some studies show improve pregnancy rate after treating the sperms with Protease enzyme to dissolve the sperm agglutination.

⊙ ICSI: the most promising, the highly effective method.

Infectious Causes of infertility

1. inflammation of testis = orchitis
2. influmation of duct system (Urethritis, epididymitis)
3. MAGI — male accessory gland infection [prostate, S. vesicle]
4. Systemic infection

① Inflammation and infection of testis: "orchitis".

* Causes: * Infection * Auto-immune orchitis * irradiation
* it may be * primary or 2ry to: epididymitis, prostatitis, Nephritis
* it affect infertility by causing defective spermatogenesis which may be temporary or permanent.

Example of orchitis is

① Mumps orchitis: viral infection of the salivary glands

- Rare affection of testis in prepubertal boys
- affection of Testis in post pubertal patients 30%
- Bilateral affection is 10-30% only.
- C/P fever, scrotal pain, swelling.
- Pathologically: it affect the Tunica Albuginea which is firm, inelastic lead to pressure, atrophy of testis.

histopathology: Sever interstitial edema + PMNL infiltration tubular hyalinization + Leydig cell hyperplasia

- U/S: Non homogenous or snow flurries picture.
- Treatment: preventive: vaccination.
  - Curative: Bed rest, elevation, Cooling of scrotum, NSAID Corticosteroid (Prednisolone) 60 mg tapered gradually
  - Surgical: early incision of tunica Albuginea and drainage of hydrocele to prevent testicular pressure and atrophy.

② Othe forms of orchitis:

Syphilis, TB, Leprosy, Bilharziasis.

② infection and inflammation of duct system < Urethritis / Epididymitis

- they are discussed in STDs
- effect on infertility:

① testicular affection: epididymitis can cause 2ry orchitis → functional infertility due to destruction of testis.

② Post-testicular affection:-

ⓐ obstructive infertility due to inflammation of epididymis, vas, ejaculatory duct.

ⓑ Immunological infertility: due to prolonged obstruction lead to back pressure on Testicular blood barrier lead to production of Antisperm antibodies.

ⓒ Ejaculatory infertility: due to urethral stricture lead to back pressure on bladder neck → incompetence → Retrograde ejaculation → Ejaculatory infertility

③ Male Accessory Gland Infection (MAGI) < prostate / Seminal vesicle

- Inflammation of prostate and S. vesicle are discussed in STDs.
- diagnoses of infertile male with prostate should include these tests for complete diagnosis.

on semen:

- Non sperm cells
- Culture studies
- Chemical studies

Effect of MAGI on infertility

- **Direct effect on sperms:**
  - Sperm damage due to secretions of micro organisms.
  - Sperm phagocytosis (spermophagy) by seminal Leucocytes plus they release lysosomal enzymes which damage the non phagocytosed sperms.
- **Disturbed accessory gland function:** MAGI can cause:
  - ↓ semen volume. - ↑ viscosity - disturbed secretory markers of prostate, S. vesicle.
- **Damaging effect of inflammatory and immunological products:**
  eg: * ROS * Anti sperm Antibodies
  * Cytokines: post inflammatory molecules secreted by activated Leucocytes ex: interferons, TNF, IL 6, 8, elastase enzyme.

they can affect on infertility by: (plus their role discussed before)

- ↓ Sperm motility
- ↑ abnormal morphology.
- ↓ sperm penetration power → ↓ pregnancy rate
- Can cause both immunologicall and obstructive infertility due to spread to ejaculatory duct → obstruction.

Treatment of MAGI:

1- **Antibiotics:** indicated in bacterial infection, Leukocytospermia.

- Doxycycline 100 mg / twice daily for 28 days is excellent Lead to eradication of Ureaplasma Urealyticum → ↑ pregancy rate.
- Some studies shows good result of doxycycline followed by trimethoprim.
- Quinolones are excellent (ofloxacin, ciprofloxacin) due to their high concentration in the prostatic tissue.

2- **Antioxidant and anti-inflammatory:**

NSAID

Antioxidants: glutathione, Acetylcystine, Catalase vit E, C improve sperm motility and sperm morphology.

(41) systemic infections and infertility

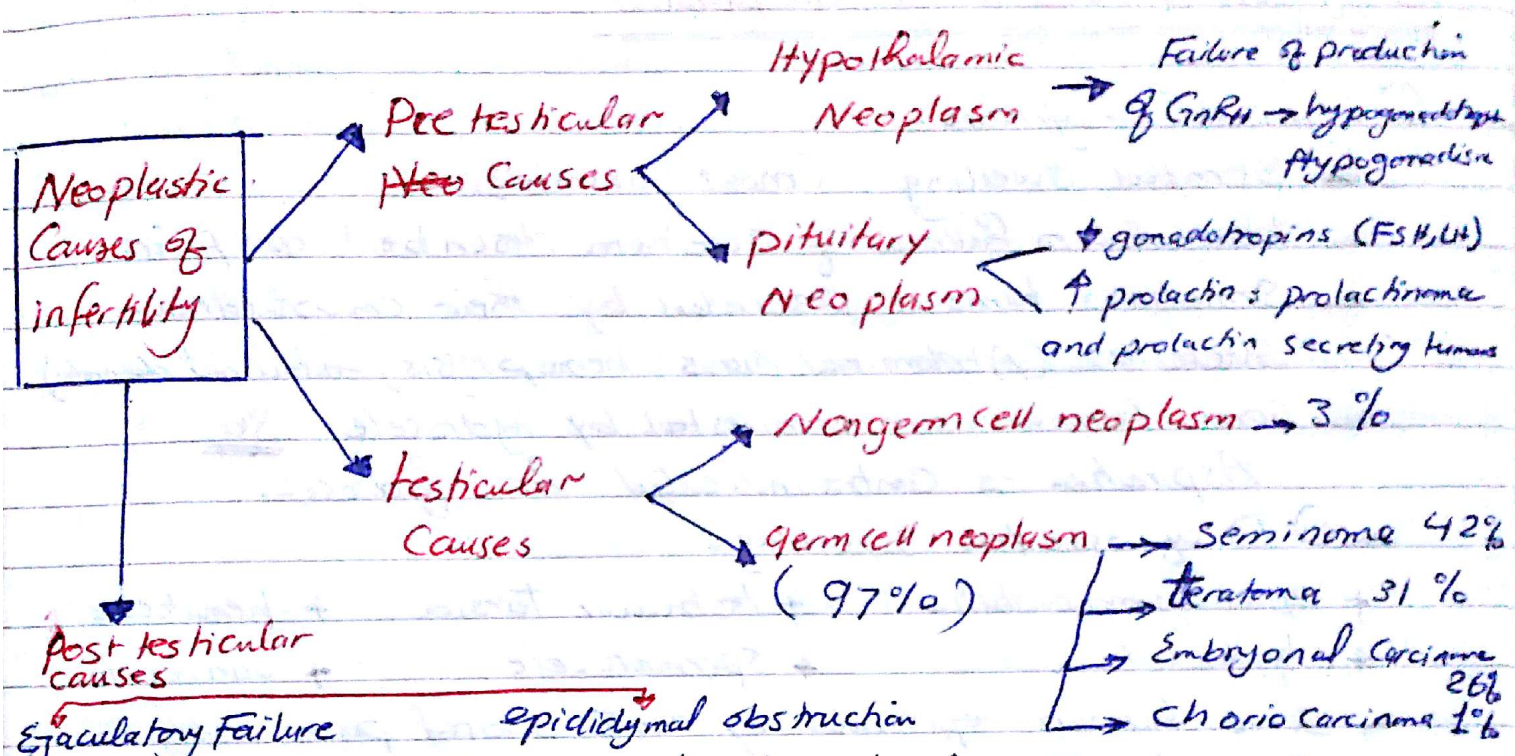
Specific infection
= AIDS =
it affect the fertility by one or more of the following mechanisms:

1- Pre-testicular: disturbance in the hypothalamic-pituitary-testicular Axis.

2- testicular damage: due to: infection, malnutrition, chemotherapy, zinc deficiency.
the testicular biopsy shows: testicular damage + interstitial fibrosis.

Non specific infection
Any systemic disease with high fever lead to suppression of spermatogenesis.

Neoplastic Causes of infertility



mechanism of infertility due to testicular Neoplasms:

- **Genetic**: there is genetic association between testicular maldescent and testicular malignancy. testicular Carcinoma is more 10 times in maldescended testis than normal descended testis.
- **Destructive effect of the tumour**: destructive spermatogenesis
  - 60 % of men with unilateral testicular tumours have sever impaired spermatogenesis
  - testicular Carcinoma in situ (CIS) at the base of seminiferous tubules show hypospermatogenesis
- **Destructive effect of the tumour therapeutics**:
  - Radio therapy: Spermatotoxic effect depend on duration, dose it affects less differentiated cells more than differentiated ie spermatogonia > spermatocytes > spermatids.
  - Chemo therapy: Spermatotoxic effect depend on dose, duration.
- **Immunological effect of the tumours**: damaging of blood testicular barrier → formation of Antisperm Antibodies.
- **Hormonal effect of the tumours**: Non germinal cell tumours (Sertoli, Leydig cells) → ↑oestrogen → triad of ED, Gynecomastia, testicular mass
  ↑ Oestrogen → distrubance of hormonal regulation of spermatogenesis

Diagnosis of testicular neoplasm:

① Clinical diagnosis:

- Scrotal swelling (most common).
- heaviness or fullness of scrotum described as pain
- Sometimes tumours presented by their complications such as (Abdominal mass, hemoptysis, endocrinal disorder)
- Some tumours are manifested by hydrocele So Aspiration is contraindicated for hydrocel.
- D.D of scrotal swelling:

+ epididymo orchitis + testicular torsion + hematocele
+ hydrocele + Spermatocele + varicocele

- Some tumours represented by acute scrotal pain with swelling similar to epididymo orchitis.

② Investigations:

- **Radiology**
  - Scrotal, Abdominal Ultrasound: to detect the nature and the location of the swelling and to detect lymphatic spread to Retroperitoneal lymph nodes.
  - CT scanning, MRI: for Abdomen, pelvis
  - X-ray Chest
- **tumour markers:** α-fetoprotein, β-HCG, Carcinoembryonic antigen, Lactate dehydrogenase.
- **Surgical exploration:** in doubtful cases.
  inguinal incision + clamping spermatic cord to prevent lymphatic or blood spread of malignant cells.

Managment of testicular neoplasms.

[1] Eradication of the tumour:

According to the stage

- Low stage disease (stage A, B_1, B_2) → Surgical excision of the testis and Nerve-sparing retroperitoneal lymph nod dissection (RPLND) followed by chemotherapy.
- High stage disease (stage B_3, C) → Chemotherapy followed by surgical excision of any residual mass if present.

[2] Preservation of Fertility:-

[a] Cryopreservation: should be done before any treatment Regardless to the quality of the sperms.

[b] Preservation of ejaculation: during RPLND to preserve the sympathetic nerves for ejaculatory reflex.

Post-testicular Causes of Neoplastic infertility.

① ejaculatory failure: occurs due to sympathetic denervation during RPLND for cancer testis or during Abdominoperineal resection for Cancer rectum.

② Epididymal obstruction: by epididymal tumours.

Medical causes of infertility

these are medical diseases or Drugs that cause infertility due to their affection on endocrine system → ED, infertility or affect ejaculation → infertility.

① Internal Factors → dissused in medical ED chapter.
② External Factors:

[A] Addiction and Abuse drugs:

Alcohol - opiates - Cannabies - Cocaine.

- Alcohol: dired effect on Liver, testis.
  - testis → peritubular fibrosis, Reduction of germ cells leading to testicular atrophy.
    Leydig cell toxin → (chemical Castration)
  - hormonal → ↓ Free testosterone due to ↑ SHBG (sex hormone binding globulin.)
    → ↑ Oestrogen Level.
  - Direct toxic effect on hypothalamus, Pituitary
- opiates: ↑ prolactin → ↓ Gonadotropins Level
- Canabis: ↓ testosterone → ↓ Sperm count
- Cocaine: ↓ Sperm count

[B] Anabolic steroids: in Athletes and body builders
have direct effect on androgens → suppression of hypothalamic pituitary - testicular axis → Azospermia, infertility

[C] Oestrogenic Compounds: that are given to cows, animals to increase their weight.
if eaten by mother → hypospadias, testicular maldescent
if eaten by male → Low sperm Count.

[D] herbicides, Insecticides:

[e] Heat exposure:

occupation eg drivers or frequent hot baths or cell phones
Fever, varicocele, spinal injuries all lead to ↓ sperm motility

[F] Heavy metals:

Cadmium, Arsenic, Lead, Mercury → disturbe the hypothalamic pituitary - testicular axis or direct testicular toxic effect.

[g] stress:

Chronic stress → ↓ GnRH and ↑ prolactin, ↓ sperm motility, ↑ abnormal forms.

[H] Smoking: → ED, ↓ sperm count, ↑ abnormal morphology.

[2] medications and therapeutics that lead to infertility: according to their sites of action

(a) Hypothalamic-pituitary testicular axis
- LHRH agonist
- High dose Corticosteroids
- Androgens and antiandrogens

(b) testis
- cytotoxic agents
- Colchicine
- Sulphasalazine
- Nitrofurantoin

(c) Epididymis → Amiodarone (antiarrhythmic)

(d) sperm motility:
- propranolol
- Quinine
- Procain
- Minocycline
- tetracycline

(e) sperm fertilization
- Nifedipine
- Allopurinole
- Colchicine
- Nicotine

Medical Treatment of infertility

① specific Rx
② Non specific Rx.

Specific Treatment

Hormonal Rx

- Hypogonadotrophic hypogonadism
  Rx Hormonal Repalcement therapy
- Hyperprolactinemia
  Rx Antiprolactin drugs (Parodel, dostenix)
- Rx of Thyroid, Suprarenal disorders

Non Hormonal Rx

Rx of Coital infertility
Rx of Immunological "
Rx of Infectious " "

Non specific treatment

Hormonal

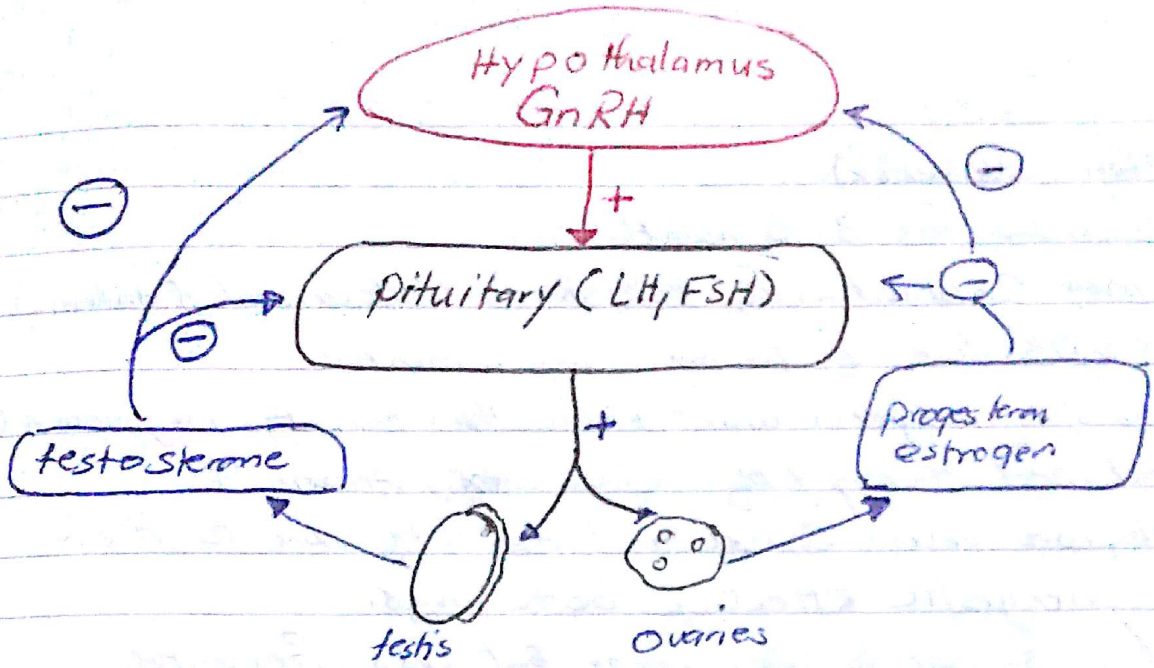
① Hypothalamic Level:
(Exogenous GnRH) (Endogenous GnRH Release) (testolactone, aromatase inhibitor)

② Pituitary Level
~~HCG~~ HCG, HMG, Growth hormone

③ Testicular level
oral androgen, Parentral androgens, Trans dermal androgens

Non Hormonal

- Reduction of testicular temperature
- improvement of testicular circulation
- Sperm protection (Antioxidant)
- Sperm Stimulation (Kinins)



Non specific treatment

II Hormonal Treatment

a) hypothalamic level: ← exogenous GnRH
← Endogenous Release of GnRH
← Testolactone.

1- Exogenous GnRH:-

exogenous administration of GnRH → ↑ LH, FSH → ↑ spermatogenesis

Dose: Intranasal 0.5mg /day

Sub cutaneous 10 µg /twice weekly.

well tolerated with minimal side effects.

2- Endogenous Release of GnRH by Antioestrogens:-

mechanism of action: Antagonize the effect of oestrogens on the oestrogenic receptors in the hypothalamus by competitive inhibition lead to inhibition of negative feed back mechanism → more release of GnRH → more FSH, LH

Drug: ① Clomiphene citrate (clomid)

- dose (25-50) mg /day for 3-6 month or daily for 25 days and rest for 5 days. every month
- it improve sperm count rather than motility or pregnancy rate
- side effects:
  - Nausea, vertigo, hair loss, visual disturbance
  - it may suppress spermatogenesis due to it's weak oestrogenic activity.

② tamoxifen (Nolvadex).

Dose: 10-20 mg for 3-6 months
it may combined with testosterone undecanoate (Andriol) but with dose of 10 mg. for 3 months.

effect: - improve in sperm count Rather than motility. Pregnancy rate
- Combined therapy of (Nolvadex, Andriol) improve sperm count and motility due to their synergistic effect of both drugs.

Side effect: similar to clomiphene But Less frequently.

3- Testo lactone (Aromatase inhibitor):

mech. of action: inhibitor of aromatization of testosterone to oestrogen ⟶ lead to ↓ the negative feed back of oestrogen on hypothalamus ⟶ ↑ GnRH, ⟶ ↑ FSH, LH.

Doses: Teslac, Arimidex (100mg) dose up to 2 gm daily for 3-6 months.

effect: improve sperm count. Some studies shows no effect on semen parameters.

NB: the aromatization of testosterone is higher more in obese patient so it can be used in obese.

⑥ pituitary Level ← HCG / HMG / Growth hormone

1- Human chorionic Gonadotrophins. (HCG)

- have (LH) activity ⟶ stimulation of Leydig cell ⟶ ↑testosterone
- dose: 1000-3000 twice weekly/IM
  Pregnyl - epifasi - choriomon.
- effect: ① improve sperm count in pt with oligozoospermia and Normal gonadotrophins Level.
  ② it's important in pt after varicocelectomy if their sperm count Less than 10 million/mL preoperatively

S.E: Acne, libido changes, Gynecomastia

2- Human menopausal Gonadotrophins (HMG):

- have FSH activity → stimulation of sertoli cell → ↑ spermatogenesis
- Dose 150 iu / 3times weekly IM. GonaLF, menogon, pregonal Fertinorm
- effect and side effect = HCG

3- Growth hormones:

action: direct action on Leydig cells.
- Stimulate releasing of Insulin like growth factor I From sertoli cell that improve spermatogenesis.

dose: 2-6 ~~IU~~ /Sc (Norditropin)

effect: improve semen parameters and pregnancy rate
other studies shows no improvement.

S.E: Reversible S.E: paraesthesia of fingers, Joint swelling
deviation of Liver function.

© testicular level: oral androgens
parentral androgens
Transdermal androgens.

1- Oral androgens:

- Androgens are the main spermatogenic hormones and some infertile males may have some defect in Androgen production or action that not obvious in routine hormonal assays.
- Mestrolone (proviron) 75-150 mg / day
- Testosterone undeconoate (Andriol) 120 mg / day.
- S.E: ~~Andro~~ oral androgens lead to feedback inhibition of the hypothalamus and pituitary gland resulting in ↓ intratesticular testosterone, Suppression of spermatogenesis
  - Jaundice, hepatitis, gynecomastia, weight gain acne.
- the most serious side effect is flaring up of prostatic Carcinoma if present.

2- Parental Androgens:

- it's used as a replacement therapy in hypogonadism.
- they were used for idiopathic infertility by mechanism of "testosterone rebound therapy" that means administration of high doses of ~~test~~ Androgens 250 mg twice weekly for about 5 month till reach Azoospermia Level. then stoppage → that may be rebound increase of hypothalamic, pituitary hormones → ↑ semen parameters. this way of treatment can cause sever damage of seminiferous tubules and premenent Azoospermia. So

No Longer used.

3- Transdermal Androgens:

more physiological way in delivering androgens because they produce serum Levels similar to the normal biological rhymes.

Non Hormonal treatment of male infertility

[1] Reduction of testicular temperature

by scrotal hypothermic device.

- pt with idiopathic infertility may have elevated scrotal temperature due to disturbed thermoregulation.
- Chronic exposure to high temperature lead to suppression of spermatogenesis and epididymal maturation
- Scrotal hypothermic device decrease the intrascrotal temperature by water evaporation → improvement of Seminal parameters and pregnancy rate.

[2] Improvement of testicular circulation → Pentoxifylline. / ~~Pentoxyfylline~~ / Terazosin.

Pentoxifylline (trental) : phosphodiestrase inhibitor (Non selective)

- it increase the sperm motility by increase intracellular cAMP → ↑ ATP → Sperm hyperactivation → ↑ motility, Count, ↑ morphology.
- it improve both testicular, epididymal microcirculation.
- Dose 1200 mg / daily for 3-6 months.
- S.E: mild : nausea, dizziness.

Terazosin hydrochloride:

- α- Blocker → Relaxation of arterial wall → improvement of testicular microcirculation and function.
- Dose: 2 mg / daily for 6 months.
- improve Count, motility
- S-E: hypotension, dizziness.

[3] Sperm protection and stimulation.

(a) Sperm protection (Antioxidants).

- protect the sperms from the oxidative damage of ROS
- Antioxidants: vit C, vit E, Glutathione, Selenium, hypotaurine
- vit E → improve Count, function
- glutathione → improve morphology, motility.

No side effects-

(b) Sperm stimulation (Kinins). < bradyKinin / Kallidin

KallikReins

are enzymes that convert Kininogen to Kinins → stimulation of sperm motility, migration through cervical mucosa.

Dose 200 IU 3 times/day / 3-6 months

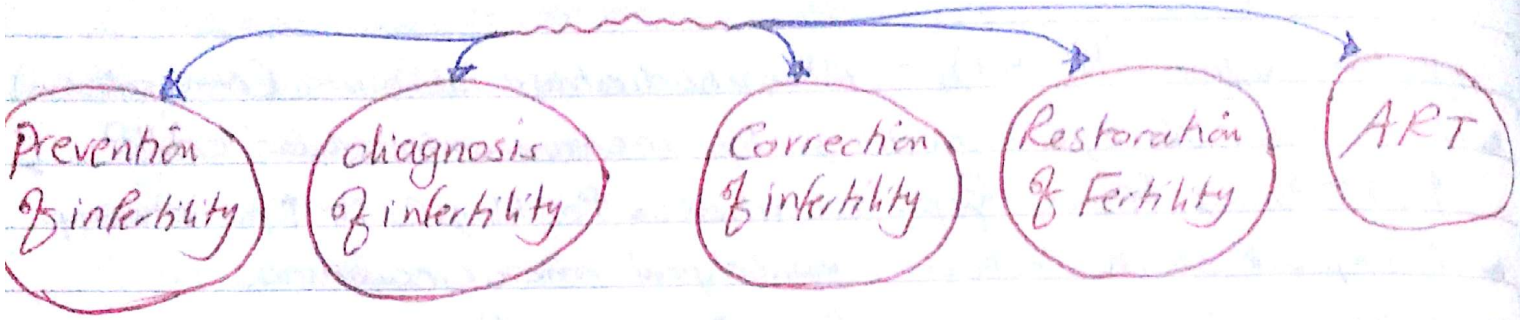
Captopril

inhibit Angiotensin converting enzyme (ACE) which is Kininase → ↑ Kinins

Dose: 50 mg / day / 3 months

Side effects: Exacerbation of any genital inflammation as: prostatitis, epididymitis so these drugs are Contraindicated.

Surgical treatment of male infertility



① Prevention of infertility by:

- orchiopexy for undescended testis to prevent high testicular temperature resulting from abnormal position
- orchiopexy for testicular torsion to prevent testicular ischemia resulting from Abnormal direction.
- Varicocelectomy for adult varicocele to prevent testicular atrophy resulting from abnormal Growth.

② Diagnosis of infertility (testicular biopsy)

③ Correction of infertility

- Varicocelectomy for adult varicocele
- Hydrocelectomy for adult hydrocele
- Correction of ductal obstruction:
  - epididymal obstruction ⟶ Epididymovasostomy
  - vasal obstruction ⟶ Vasovasostomy
  - Ejaculatory duct obstruction ⟶ Transurethral resection

④ Restoration of fertility:

Vasovasostomy for reversal of vasectomy.

⑤ ART:

operations for sperm Retrieval for the use of different procedures for gametes micromanipulation.

Testicular Biopsy

Indications :

[1] Diagnostic

- Azoospermic patient with normal size testis to differentiate between Germ cell pathology (Abnormal spermatogenesis) and ductal obstruction (Normal spermatogenesis).
- Sever oligozoospermia Less than 5 million/mL to exclude partial obstruction
- testicular malignancy. biopsy is taken from the contralateral testis to exclude Carcinoma in situ.
- Diagnosis of testicular failure.

[2] therapeutic

micro TESE indicated for ICSI.

Complication of biopsy

- Epididymal injury
- Vascular injury → haematoma.
- High titre of Antisperm Antibody in some patients.

Testicular Sperm Retrival :

[1] Testicular sperm extraction (TESE). open

it is a technique to extract the sperms ~~during~~ from testis during x testicular biopsy. it gives definitive diagnosis.

indications : ▷ Funchon Azoospermia ▷ Necrozospermia
▷ Failure of Epididymal Retrival.

- if there's any spermatogenic foci found it's used for ICSI.
- Micro TESE should be done at least 6 month interval.
- Y chromosone microdeletion with AZF b region has no chance for TESE.
- the more the histopathologically spermatogenic impairment the Lesser Chance for TESE.

[2] Testicular sperm Aspiration : ((TESA))

it's a technique in which the sperms are aspirated from the testis through a fine needle. it's lesser effective than open testicular biopsy for TESE in collecting sperms specially in functional Azoospermia.

3] Rete testis Aspiration (RETA)

Technique in which the sperms are aspirated from the region of Rete testis, used in obstructive Azoospermia.

Epididymal Sperms Retrival:

1. Microsurgical epididymal sperm Aspiration (MESA).
   - the sperms are collected microsurgically by incision of epididymal tubule then aspirated into capillary tube.
   - if there's No motile sperms → proximal tubules are incised till the sperms are found.
   - Cryopreservation is advised to avoid Repeated Surgery.
   - indication of MESA → Congenital bilateral absent of vas.
     → Uncorrectable epididymal obstruction
2. Percutaneous epididymal sperm aspiration (PESA)
   the same indication of MESA. the epididymal sperms are collected using a small needle introduced into the scrotal skin (Percutaneous) to which suction is connected.
   PESA is more simple than MESA but may cause more damage.
3. Spermatocele Aspiration: SPAS
   epididymal simple needle Aspiration.

Indicated in obstructive Azoospermia due to epididymal cyst (Spermocel)

Indication of ICSI

according to the way of obtained sperms (Ejaculate, epididymis testicular or Cryopreserved.

1. Ejaculated Sperms:-
   - a) Sperm disorders: → Abnormal parameters ↓ Count, motility ↑ abnormal forms
     → Abnormal sperm structure (Immotile Cilia S, Globozoospermia)
   - b) Sperm Antibodies: IgG, IgA:
     these interfers with: Sperm transport
     Sperm-ovum interaction
     Embryo development.

(c) Sperm ejaculation disorders:
- ▷ Premature ejaculation.
- ▷ Absent of ejaculation (Azospermia) due to:
  - defect in sperm production (Androgen deficiency)
  - Sever inflammation → Fibrosis of gonads.
- ▷ Anejaculation Congenital: → (Congenital Anorgasmia)
  Acquired: (Drugs, operations, spinal injury)
- ▷ Retrograde ejaculation.

(d) Sperm fertilization disorders:
- ▷ ↓ Sperm mucous interaction
- ▷ ↓ Sperm Capacitation.
- ▷ defect in Zona binding, acrosomal reaction.
- ▷ defect in Sperm - ovum interaction
- ▷ Repeated Failed IUI, IVF.

(2) Epididymal sperms:
(a) Uncorrectable ductal obstruction, due to Congenital bilateral Absence of vas deferens.
(b) Failed correction of ductal obstruction:
Failed epididymo vaso stomy, Failed vaso vaso stomy
Failed Trans urethral resection of ejaculatory duct obstruction

(3) Testicular sperm:
- ▷ Primary testicular failure: eg ← hypospermatogenesis, spermatogenic arrest, Klinefelter syndrome.
- ▷ Necrozoospermia
- ▷ failure of epididymal sperm recovery.

(4) Cryo preserved sperms.